A STUDY ON PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH NEWLY DIAGNOSED DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

Submitted to

The Tamil Nadu Dr.M.G.R.Medical University

M.D. DEGREE EXAMINATION

BRANCH – I (GENERAL MEDICINE)

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2011

BONAFIDE CERTIFICATE

This is to certify that **"A STUDY ON PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH NEWLY DIAGNOSED DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE"** is a bonafide work done by **Dr. Anuja.R** post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D.Degree Branch I (General Medicine)** during the academic period from May 2008 to April 2011.

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ACKNOWLEDGEMENT

I sincerely thank. **Dr. V.Kanagasabai, M.D.**, Dean, Kilpauk Medical College, Chennai for permitting me to utilize the facilities needed for this dissertation work.

I am extremely grateful to **Prof.Dr.G.Rajendran, M.D.,** Professor and Head of the Department, of Internal Medicine, Kilpauk Medical College and Hospital for permitting me to carry out this study and for his constant encouragement and guidance.

I owe my sincere gratitude to my Chief **Prof. D.Varadharajan M.D.,** Professor, Department of Internal Medicine, Kilpauk Medical College for his esteemed guidance and valuable suggestions in all the stages of this dissertation.

I also express my sincere gratitude to **Prof. N.Raghu,M.D., Prof. M.D.Selvam,M.D., Prof.B.Chellam, M.D.,** for their help and guidance rendered during the entire period of my work.

I wholeheartedly express my sincere thanks to **Prof.C.R.Anand Moses, M.D., Head of Dr. Ambedkar Institute of Diabetology**, Kilpauk Medical College, Chennai for his valuable guidance, help and support throughout my dissertation work.

I wholeheartedly express my sincere thanks to **Prof. Lakshminarasimhan, M.D., D.M., Head of the Department of Neurology**, Kilpauk Medical College, Chennai for his valuable help, timely suggestions and support throughout my dissertation work.

I wish to thank **Dr.Kulothungan.M.D., Dr.Siddharthan.K.M.D., Dr.Venkateswaralu.M.D., Dr.Radha M.D.,and Dr.Shanthi, M.D.,** Assistant Professors, Department of Medicine, Kilpauk Medical College for their valuable suggestions and help rendered throughout this work.

I am grateful to **Dr.Suresh, M.D.D.Diab, Dr.Shanmugam MD D.Diab.,** Assistant Professors in the Department of Diabetology, Kilpauk Medical College for the advice and help rendered to me.

I also extend my thanks to all the laboratory technicians and Statistician in Diabetology Department for their valuable support throughout my dissertation work.

I also thank my parents, colleagues, friends and staff of our hospital, for their support of this work.

Last but not the least, with sincere gratitude, I thank all the patients who contributed so much to this study without whom this study could not have been possible.

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INTRODUCTION

Diabetes mellitus is characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. When fully expressed, diabetes is characterized by fasting hyperglycaemia but when less overt is recognized by glucose intolerance.[1]

Diabetes is known to effect different organs in the body especially the eyes, kidneys, heart & nerves. It is these microvascular and macrovascular complications which are most troublesome.

Diabetes has emerged as a major healthcare problem in India with an estimated 50.7 million diabetics[2] according to data published by international diabetic federation (2nd only to China[2]) and it being predicted to increase to 79.4[3] million people by the year 2030. It is estimated that by 2030 every fifth person with diabetes will be an Indian[4]. Due to these sheer numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates that diabetes, heart disease and stroke together will cost about $ 333.6 billion over the next 10 years in India[4].

Neuropathy is one of the earliest and most common chronic complications of diabetes[5]. For some patients, the condition is simply an annoyance and results in occasional numbness and tingling here and there. But neuropathy can forebode infection, loss of a limb, and even death as a result of peripheral neuropathy and vascular disease, and dangerous disturbances in blood pressure, nutrition, and urinary tract function. It can also be a source of heartbreak, since, in conjunction with peripheral vascular disease, it causes impotence and incontinence. Thus, diabetic neuropathy can affect a wide spectrum of systems with varying degrees of severity.

Because of this it is imperative that we understand the prevalence as well as risk factors for diabetic neuropathy in different stages of glucose tolerance so that appropriate steps may be adopted for early diagnosis, treatment and prevention of complications.

The present work is a modest endeavour to find the prevalence of neuropathy in our population and find the risk factors associated with it.

AIM & OBJECTIVES

1) To determine the prevalence of peripheral neuropathy in newly diagnosed drug naive type 2 diabetes mellitus.

2) To determine the prevalence of peripheral neuropathy in impaired glucose tolerance patients.

3) To determine the risk factors for the same in the above mentioned populations

DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

HISTORY

The history of diabetes is as old as that of medicine. Early evidence of description of symptoms of diabetes has been recorded in the Ebers papyrus, 1550 BC[6]. Arateus (30-90AD) coined the term diabetes, meaning “siphon” to explain the “liquefaction of flesh and bones into urine”. In Greek it means “to run through” that describes the “unquenchable thirst” seen in association with this disease[7]. Shushruta (Circa 600 AD) noted this disease in Ayurveda and described it as “madhumeha”[8].

In 1869, Paul Langerhans, in his dissertation on pancreatic histology described “clumps of cells” which were named the islets of langerhans shortly after his death[9, 10]. In 1889, Minkowski and Von Mering, in Strassburg, Germany discovered the central role of insulin of pancreas in diabetes[11]. In 1910 Jean

de Meyer suggested that the pancreatic secretion lacking in diabetic state be called “insulin” to denote its origin from the insulae of Langerhans[12]. Banting and Charles Best in 1921, extracted insulin from dogs’ pancreas[13].The first chemical application of insulin was on a 14yr old boy, Leon Thompson, a patient with diabetic ketoacidosis in January 1922 Canada. This revolutionized the management of diabetes mellitus. Oral hypoglycaemic drugs were introduced by Frank and Fuchs in 1955[6].

DIABETES AS WE KNOW IT

When fully expressed, diabetes is characterized by fasting hyperglycaemia, but the disease can also be recognized during less overt stages, most usually by the presence of glucose intolerance. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, and polyphagia, and in its most severe forms, with ketoacidosis or nonketotic hyperosmolar state, which, in the absence of effective treatment, leads to stupor, coma and death. However the catch in the story of diabetes mellitus is that, hyperglycaemia sufficient to cause pathologic functional

changes is often present for a long time before the diagnosis is made.

Table- 1 CLASSIFICAITON OF DIABETES MELLITUS[1]

Type 1 (ß cell destruction, usually leading to absolute insulin deficiency) A. Autoimmune B. Idiopathic
Type 2 (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)
Other specific types
Genetic defects of β-cell function
Genetic defects in insulin action
Diseases of the exocrine pancreas
Endocrinopathies
Drug- or chemical-induced
Infections
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes

Type 1 Diabetes mellitus

Type 1 diabetes is the form of the disease primarily due to β-cell destruction. This usually leads to a type of diabetes in which insulin is required for survival[14]. Type 1 diabetes usually

is characterized by the presence of anti-GAD, anti-islet cell or anti-insulin antibodies, which reflects the autoimmune processes that have led to β-cell destruction (type 1A)[15,16]. However, particularly in non whites, type 1 diabetes can occur in the absence of autoimmune antibodies and without evidence of any other autoimmune disorder (type 1 B or idiopathic).

Type 2 Diabetes Mellitus

Type 2 diabetes is the most common form of diabetes. Patients with type 2 diabetes usually have insulin resistance and relative, rather than absolute, insulin deficiency. The specific aetiology of this form of diabetes is not known .At the time of diagnosis of diabetes, and often throughout their lifetimes, these patients do not need insulin treatment to survive, although ultimately many may require it for glycemic control. This form of diabetes is associated with progressive β-cell failure with increasing duration of diabetes[17].Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycaemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes. However, such patients are at increased risk of developing macrovascular and microvascular complications.

Impaired glucose tolerance

IGT is a stage of impaired glucose regulation that is present in individuals whose glucose tolerance is above the conventional normal range but lower than the level considered diagnostic of diabetes . IGT cannot be defined on the basis of fasting glucose concentrations; an OGTT is needed to categorize such individuals[18]. Persons with IGT do have a high risk of developing diabetes, although not all do so. Some revert to normal glucose tolerance, and others continue to have IGT for many years. But studies have shown that most patients with impaired glucose tolerance move towards greater glucose dysequlibrium (DPP study) [19]. Persons with IGT have a greater risk than persons of similar age with normal glucose tolerance of developing arterial disease[20]. Although initially thought not to be associated with microvascular complications recent studies show significant prevalence[19].

Impaired fasting glucose

IFG is also a stage of impaired glucose homeostasis. This category was introduced in the 1997 ADA and 1999 WHO classifications[15, 16] to include individuals whose fasting glucose levels were above normal but below those diagnostic for

diabetes. If an OGTT is performed, some of these individuals will have IGT and some may have diabetes. Consequently, it is prudent, and recommended by WHO, that such individuals, if possible, have an OGTT to exclude diabetes. Although both categories contain individuals with a high risk of progressing to type 2 diabetes[20,21,22,23] the proportion with IFG in most populations is smaller than that with IGT.[24]

Criteria for the diagnosis of Diabetes Mellitus*[25,26,27]

(1) $HbA_1C \geq 6.5\%$ **or**

(2) Fasting plasma glucose $\geq$ 126 mg/dl **or**

(3) 2-hr plasma glucose $\geq$ 200 mg/dl post 75g oral glucose challenge **or**

(4) Random plasma glucose $\geq$ 200 mg/dl with symptoms (polyuria, polydypsia, and unexplained weight loss)

*For criteria 1-3: Repeat test to confirm unless symptoms are present. It is preferable that the same test be repeated for confirmation. If two different tests are used (e.g., FPG and A1C) and both indicate diabetes, consider the diagnosis confirmed. If the two different tests are discordant, repeat the test above the diagnostic cut point.

Criteria for Pre-diabetes[25,26,27]**

(1) Fasting plasma glucose 100 – 125 mg/dl [Impaired fasting glucose (IFG)] **or**

(2) 2-hr post 75g oral glucose challenge 140 – 199 mg/dl [Impaired glucose tolerance (IGT)] **or**

(3) HbA1C 5.7 % – 6.4 %

**For all tests, risk of diabetes is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Screening for Diabetes Mellitus-

Consider screening for diabetes mellitus in any adult with BMI ≥ 25 with 1 or more risk factors for diabetes. Otherwise start at the age of 45(if normal repeat testing every 3yrs).

Monitor for diabetes development annually in all pre diabetics.

Use risk factor analysis: Screen for overt diabetes in high risk patients, pregnant women in early pregnancy, prior GDM, prior delivery of LGA baby, PCOS, glucosuria, strong family history of type 2 diabetes mellitus.

Screening for Diabetic Neuropathy

At diagnosis and annually

Feet examination every three months.

DIABETES AND NERVOUS SYSTEM

"The era of coma has given way to the era of complications."

—Elliot P. Joslin

Of all the long-term complications of diabetes, none affects so many organs or systems of the human body as the group of conditions that are included under the term diabetic neuropathies. The frequency with which diabetes affects the nervous system and the diverse manifestations might well explain the belief till the middle of the 19th centuary[28] that diabetes was the consequence rather than the cause of nerve dysfunction.

Peripheral neuropathies have been described in patients with primary (type 1 and type 2) and secondary diabetes of differing causes, suggesting a common etiologic mechanism based on chronic hyperglycaemia. The pivotal role of hyperglycaemia in the pathogenesis of neuropathy has received strong support from landmark studies such as the Diabetes Control and Complications Trial (DCCT) [29, 30] and the United Kingdom Prospective Diabetes Study (UKPDS)[31.]. Neuropathies are characterized by a progressive loss of nerve fibres that can be assessed noninvasively by a variety of methods, varying from a structured neurologic examination through quantitative sensory testing to detailed electrophysiology (EP) and autonomic function testing.[32]

HISTORY

The first clinical description of diabetic peripheral neuropathy was given by Rollo in 1798, when he described the paraesthesias and pain in the foot of a diabetic patient. However it was Marchal de Calvi in France who recognized the true nature of the condition in 1864.[33,] Later, Charcot extended these observations as well as described (initially in syphilis) the neuroarthropathy which has now come to be named after him.[34] Davies-Pryce, a surgeon working in Nottingham, England, was the first to recognize the link between diabetic neuropathy and foot ulceration.[35] It was not until the twentieth century, however, that autonomic neuropathy in diabetes was first reported.[36]

DEFINITIONS AND CLASSIFICATION

Although there have been previous classifications based on pathologic and etiologic considerations, it has become increasingly clear that, causative mechanisms resulting in neuropathy are multiple and complex. So a clinical or descriptive classification of the neuropathies is favoured.[32, 37]. Even in this area, a number of classifications exist. Examples include the purely clinical descriptive classification proposed by Boulton and Ward[38] and that based on potential reversibility together with clinical description [32, 39]

Descriptive Clinical Classification of Diabetic Neuropathies (Table-2)[38]

Poly neuropathy	**Mononeuropathy**
Sensory - Acute sensory Chronic sensorimotor Autonomic Proximal motor Truncal	Cranial Isolated peripheral Mononeuritis multiplex Truncal

Classification Based on Potential Reversibility (Table – 3) [39,40]

Rapidly reversible :	Hyperglycaemic neuropathy
Persistent symmetrical :	Sensorimotor (Chronic) Acute Sensory Autonomic
Focal and multifocal :	Cranial Thoracoabdominal radiculopathies Focal limb Amyotrophy (Proximal motor) Compression/entrapment
Superimposed Chronic Inflammatory Demyelinating Polyneuroapthy (CIDP)	

The San Antonio consensus defined diabetic neuropathy as "a demonstrable disorder clinically evident or subclinical, occurring in the setting of diabetes without non diabetic causes, including manifestations in the somatic and/or autonomic parts of the peripheral nervous system."[41,] The Rochester Diabetic Neuropathy Study established a paradigm for clinical trial design.[42,43]. The following were assessed: (1) neuropathic symptoms (neuropathy symptom score, NSS), (2) neuropathic deficits (neuropathy impairment score), (3) sensorimotor nerve conduction velocity, (4) quantitative sensory tests, and (5) autonomic function tests. The minimum criteria for a diagnosis of neuropathy required two or more abnormalities among the listed criteria. Staging was as follows: N0 = no neuropathy, minimum criteria unfulfilled; N1 = asymptomatic neuropathy (NSS = 0); N2 = symptomatic neuropathy; N3 = disabling neuropathy.

EPIDEMIOLOGY

The quality and even quantity of epidemiologic data on diabetic neuropathy remain poor for a number of reasons, including inconsistent definitions, poor ascertainment, lack of population based studies, and failure to exclude non diabetic neurologic disease[32,37,44]. The available data show a wide variation in the prevalence of diabetic neuropathy. The population-based studies (western) showed a high prevalence, suggesting that at least half of older, type 2 diabetic patients had significant

neuropathic deficits and hence were at high risk for insensitive foot ulceration.[45].However neuropathy may be present at diagnosis in type 2 diabetes. The prevalence was 4-6 times greater in clinically newly diagnosed diabetic subjects (14-43%) compared to normal people [46,47.48]. More disturbing than this is the increasingly reported data regarding the prevalence of neuropathy in patients with impaired glucose tolerance suggesting that neuropathy begins to emerge in the prediabetic stage. The lack of longitudinal studies makes this increased prevalence in IGT patients controversial.

Table--4

STUDY / COUNTRY	NORMAL	NEW DIABETIC	IGT	KNOWN DIABETIC
Ratzmann et al [46]		14.7%		
Partenan et al[47]	2%	8%		
Franklin (SLV)[49]	3.5%		11.2%	
Hoorn[48]	.5%	16%	43.3%	68.5%
Young et al (UK)[50]				28.5%
*Dyck et al (US)[42]				47.6%
*Kumar et al(UK)[45]				41.6%
*Zeigler et GER)[51]				28%
Pradeepa et al[52]		19.5%		27.8%

Certain prospective studies have assessed risk factors for the development of neuropathy. The DCCT and UKPDS demonstrated a clear relationship between poor glycemic control and the development of neuropathy. In addition to glycemic control, Adler and co-workers [53] identified height, age, and alcohol intake as significant risk factors for neuropathy in a study of U.S.Veterans. Other studies have identified ischemic heart disease, smoking, and diabetes duration as being independently related to neuropathy [54]. In the Eurodiab prospective study, in addition to hyperglycaemia, independent risk factors that predicted the development of neuropathy included BMI, hypertension and deranged lipids.[55]

CLINICAL FEATURES

Focal and Multifocal Neuropathies

A number of characteristic focal and multifocal neuropathies, none of which are unique to the diabetic patient, occur in diabetes; together, they account for no more than 10% of all the neuropathies. Most of these tend to occur in older, type 2 patients and is often painful but the prognosis is generally good with the patients making complete or partial recovery. The rapid onset of symptoms and signs in most cases, together with the focal nature of the deficits, is suggestive of a vascular aetiology.

Cranial Mononeuropathies - Diabetic ophthalmoplegia (third nerve palsy) is the commonest, and may be of relatively rapid onset, presenting with pain in the orbit, diplopia, and ptosis. It may also involve the the 5th and the 4th cranial nerves.

Isolated and Multiple Mononeuropathies - A number of nerves are prone to pressure damage in diabetes; by far the most common is the median nerve as it passes under the flexor retinaculum resulting in carpal tunnel syndrome (CTS). In the Rochester Diabetic Neuropathy Study, 30% of patients had EP evidence of median nerve compression, although only fewer than 10% had characteristic symptoms[42]. Other, less frequently seen entrapment neuropathies may involve the ulnar nerve, the lateral cutaneous nerve of the thigh (meralgia paresthetica), the radial nerve (wrist drop), and the peroneal nerve (foot drop). Occurring in isolation, most of the above (except foot drop) carry a good prognosis with recovery, although surgical decompression may be required. Mononeuritis multiplex simply describes the occurrence of more than one isolated mononeuropathy in an individual patient.

Truncal Neuropathies - Truncal neuropathy is typically characterized by pain occurring in a dermatomal band like distribution around the chest or abdomen. The pain may be severe and have the characteristics of both nerve trunk pain and dysesthesias. Thus, the patient may experience dull, aching, boring pain together with burning discomfort or allodynia. EP

investigation, including needle electrode electromyography, is useful and can be diagnostic. Truncal neuropathies may occasionally present with motor manifestations, typically a unilateral bulging of abdominal muscles that is usually associated with pain as described[56]. Prognosis is good and recovery is the rule.

Proximal Motor Neuropathy -Typically affecting older, male, type 2 diabetic patients, proximal motor neuropathy (amyotrophy) presents with pain, wasting, and weakness in the proximal muscles of the lower limbs, either unilaterally or with asymmetrical bilateral involvement. In addition, there is often a distal symmetrical sensory neuropathy, and weight loss of as much as 40% of premorbid body mass may occur.[57] Buckling of knees and difficulty in climbing stairs are typical symptoms. The aetiology of diabetic amyotrophy is probably a polyradiculopathy. Recovery is gradual.

Chronic Inflammatory Demyelinating Polyneuropathy - A demyelinating neuropathy meeting the electrophysiologic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) has been increasingly recognized to occur more commonly in patients with both type 1 and type 2 diabetes.[58] The clinical picture is of a symmetrical, predominantly motor polyneuropathy with proximal and distal weakness in the lower limbs with reduced reflexes that has a progressive course. Because patients with CIDP might respond to immunomodulatory therapy,

it is important to distinguish this condition from other diabetic neuropathies, particularly proximal motor neuropathy. Therefore, CIDP should be suspected in neuropathic diabetic patients in the following cases: 1. A predominance of motor signs involving proximal or distal lower limb muscles.2. After some years of distal sensory neuropathy, a motor neuropathy develops with progressive symptoms and signs. 3. A patient is diagnosed with proximal motor neuropathy (amyotrophy).

Symmetrical Neuropathies

Autonomic Neuropathy – The autonomic nervous system, which controls a wide range of bodily functions, can be damaged in diabetes with a variety of manifestations, most commonly cardiovascular, urogenital, gastrointestinal, thermoregulatory, and sudomotor function.[59]

Cardiovascular - Cardiac autonomic neuropathy manifests initially as an increase in heart rate secondary to vagal denervation followed by a decrease due to sympathetic denervation; finally, a fixed heart rate supervenes, which responds only minimally to physiologic stimuli. Postural hypotension is common due to efferent sympathetic denervation.

Gastrointestinal - Autonomic neuropathy of the gastrointestinal system manifests as an abnormality in motility, secretion, and absorption. Clinically, patients present with two major problems: diabetic gastroparesis, manifested by nausea, postprandial vomiting, and alternating

nocturnal diarrhea and constipation.[59] The diagnosis and treatment of these abnormalities represent an extremely difficulty.

Erectile Dysfunction - ED resulting from autonomic dysfunction is usually progressive but of gradual onset and progression.[59].The patients may also have retrograde ejaculation.

Bladder Dysfunction - Bladder dysfunction is also well recognized as a consequence of autonomic neuropathy in some patients; this "cystopathy" is usually the result of neurogenic detrusor muscle abnormality. In extreme cases, gross bladder distension may occur with abdominal distension and overflow incontinence.

Sweating Abnormalities - Abnormalities of sweating are common but often neglected[60]. Most common is reduced sweating in the extremities, particularly the feet, which is a manifestation of sympathetic dysfunction. In contrast to the dry feet, some patients complain of drenching truncal sweating, particularly at night. Gustatory sweating, which is profuse sweating in the head and neck region on eating certain foods, is a highly characteristic symptom of diabetic autonomic neuropathy that is also common in patients with nephropathy and is "cured" by renal transplantation.[61]

Distal Sensory Neuropathy Distal sensory neuropathy is the most common of all the diabetic neuropathies. It is a diffuse symmetrical disorder, mainly affecting the hands and legs in a glove and stocking

distribution. It is often accompanied by motor symptoms (sensorimotor neuropathy).

The onset of sensory neuropathy is insidious and symptoms that may be intermittent in the early stages. However, some patients have a rapid onset of painful symptoms. This latter type, often follows a period of severe metabolic instability (hyperglycaemic neuropathy) or may be precipitated by a sudden improvement of control ("insulin neuritis"),[62] The symptoms in this type are usually severe, whereas there may be few if any clinical signs, and quantitative testing may be normal.

The neuropathic symptoms may be difficult for the patient to describe but typically fall into a recognizable pattern, ranging from the severely painful (or positive) at one extreme, with burning pain, stabbing, and shooting sensations; uncomfortable temperature sensations; paraesthesias, hyperaesthesias, and allodynia; to mild or "negative symptoms," such as decreased pain sensation, deadness, and numbness. Symptoms fluctuate with time and are prone to nocturnal exacerbation with bedclothes hyperesthesia. Another relatively common complaint in neuropathy is that of postural instability; diabetic neuropathic patients report more falls, and unsteadiness (secondary to disturbances in proprioception). Although neuropathic symptoms are predominantly if not exclusively sensory, in many cases the signs are both sensory and motor, with sensory loss in a stocking distribution, together with minor degrees of

small muscle wasting and occasionally weakness. The ankle reflex is usually reduced or absent. Because some neuropathic patients may be asymptomatic, it is essential that all diabetic patients have their feet examined on a regular basis.[37]

Small-Fibre Neuropathy - This shares many similarities with the acute sensory neuropathy, but symptoms tend to be more persistent. However, this may simply represent an early stage in the development of chronic sensorimotor neuropathy.[63]. *Recently, a similar predominantly small-fiber neuropathy often with severe painful symptoms, has been observed in patients with Impaired Glucose Tolerance (IGT[64]). The patients with IGT may also have features of large fibre involvement.*

PATHOGENESIS

The pathogenesis of peripheral neuropathy is complex and involves the interaction of several factors. Given below is a brief discussion of the contributing factors.

Hyperglycaemia

In type 2 diabetes, longitudinal data from the Rochester cohort supports the contention that the duration and severity of exposure to hyperglycemia are related to the severity rather than the onset of neuropathy.[65] Studies in patients presenting with symptoms of a small fibre neuropathy suggest an increased prevalence of impaired glucose tolerance (IGT) in these patients, suggesting a glycemic threshold below the current

definition of diabetes above which polyneuropathy develops[66]. However, in a recent population based study the prevalence of polyneuropathy was 28.0% in diabetic subjects and only 13.0% in those with IGT, 11.3% in those with impaired fasting glucose (IFG) compared to 7.4% in those with normal glucose tolerance (NGT), indicating a minimal contribution of hyperglycemia.[67] This may indicate that other factors other than hyperglycaemia may contribute to the pathogenesis. With regard to the effects of intervention, the data supportive of benefit with improving glycemic control is controversial. While the UKPDS and the DCCT study showed improvement and blunted progression of neuropathy with glycemic control, the VA cooperative study in type 2 diabetic patients, 153 patients who were randomized to intensive versus conventional therapy achieved a 2.07% difference in HbA1c over 2 years but failed to demonstrate a significant difference in the progression of either somatic or autonomic neuropathy.[68] Similarly, the Steno-2 study which implemented multifactorial intervention, including improved glycemic control, improved autonomic but not somatic neuropathy[69,70].

Polyol Pathway Abnormalities

The excess glucose is metabolised by aldose reductase to form sorbitol and the latter by the action of sorbitol dehydrogebnase is converted to fructose. The excess sorbitol decreases the intracellular levels of

myoinositol which in turn decreases the activity of Na- K ATPase activity. This results in structural and functional abnormalities of nerves[71].

Animal models of diabetes consistently demonstrate an association between increased flux through the polyol pathway and a reduction in NCV, both of which can be ameliorated with aldose reductase inhibitors (ARIs)[72]. An early meta-analysis of randomized controlled trials of ARIs, only demonstrated a small but statistically significant reduction in decline of median and peroneal motor nerve conduction velocity[73].

Glycation

Hyperglycaemia induces the formation of advanced glycation end products (AGEs) on peripheral nerve myelin which contributes to segmental demyelination by increasing its susceptiblity to phagocytosis by macrophages. Also it modifies axonal cytoskeletal proteins such as tubulin, neurofilament, and actin resulting in axonal atrophy and degeneration but reduced regeneration due to glycation of laminin.[74] However, in a primate model of type 1 diabetes, 3 years of treatment with aminoguanidine (agent which prevent the formation of AGE) did not restore conduction velocity or autonomic function[75]. It is becoming increasingly apparent that many drugs that are currently used for other indications including pioglitazone, metformin[76], angiotensin-converting enzyme (ACE) inhibitors and ATII antagonists may act as powerful antiglycating agents.

Oxidative Stress -

A considerable body of data supports the role of oxidative stress in the pathogenesis of diabetic neuropathy in animal models[77]. AGE or Amadori products, reacts with receptors for AGE (RAGE). This binding induces a cascade of signalling events leading to the production of reactive oxygen species (ROS)[78,79]. The ROS in turn acts on the lipids forming lipid peroxides which are directly toxic to the cells[80]. On dividing cells it results in DNA mutations and genomic instability[81]. On non dividing cells like neurons the damage to proteins and lipids make them dysfunctional and unable to perform normal axonal transport and signalling [82]. Hence increasing antioxidant potential is an attractive treatment strategy. Short term benefits have been observed with intravenous alpha-lipoic acid (LA), a powerful antioxidant that scavenges hydroxyl radicals and superoxide and peroxyl radicals and regenerates glutathione.[83]

Poly (ADP-Ribose) Polymerase-1 (PARP)

Increased oxidative and nitrosative stress activates the nuclear enzyme, poly(ADP-ribose) polymerase-1 (PARP) which depletes its substrate, NAD+, slowing the rate of glycolysis, electron transport, and ATP formation and inhibits GAPDH by poly (ADP-ribosy)lation.[84] These lead to a deleterious effect on nitrergic (NO) innervation, contributing to autonomic neuropathy.

C Peptide

Impaired insulin/C peptide action has emerged as a prominent factor in the pathogenesis of the microvascular complications in type 1 diabetes. Experimental studies have demonstrated a range of actions that include effects on expression of neurotrophic factors, regulation of molecular mechanisms underlying the degeneration of the nodal apparatus, as well as DNA binding of transcription factors leading to modulation of apoptosis.[80] C-peptide has been proposed to prevent and reverse myelinated nerve degeneration of the node and paranode and unmyelinated nerve axonal degeneration, atrophy, and loss.[85].

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) regulates angiogenesis and neuronal survival by stimulating neurons and glial cells to survive and grow. Thus, with its potential for a dual impact on both the vasculature and neurons, it could represent an important therapeutic intervention in diabetic neuropathy. To date, a therapeutic benefit in diabteic neuropathy has been demonstrated for VEGF in experimental studies only.

Neurotrophins

Neurotrophins promote the survival of specific neuronal populations by inducing morphologic differentiation, enhancing nerve regeneration, stimulating neurotransmitter expression, and altering the physiologic characteristics of neurons. Thus modulating neurotrophic support

represents an alternative approach to the treatment of diabetic neuropathy, that is the stimulation of repair without necessarily addressing the underlying cause of nerve damage.

Mitogen-Activated Protein Kinase

Upstream inducers and transducers signal transcriptional and translational abnormalities through effector molecules referred to collectively as the mitogen-activated protein kinase (MAPK) family, which mediate early gene responses and aberrant phosphorylation of neurofilaments, which are major constituents of the axonal cylinder[86]. Thus, any abnormality in synthesis, delivery, or processing of these critical proteins could lead to impairments in axon structure and function[87].

PATHOLOGY

Detailed morphometric studies of sural nerve biopsies provide considerable insights into the underlying pathology and pathogenesis of diabetic neuropathy. A significant abnormality in both myelinated and unmyelinated fibres occurs despite entirely normal clinical and neurophysiologic tests of neuropathy.[88,89,90]

Myelinated Fibres -The hallmark of advanced diabetic neuropathy is loss of myelinated fibers[88.]

Unmyelinated Fibres- Axonal degeneration with active regeneration of unmyelinated fibres occurs early in the evolution of neuropathy prior to axonal degeneration of the myelinated fibres,[91] but importantly, their

regenerative capacity is maintained long after the myelinated fibres have lost their capacity to regenerate [92,93]

Autonomic Tissue- Pathologic studies of autonomic tissue are limited to post-mortem or surgical material. In patients with diabetic gastropathy, the vagus nerve shows a reduction in myelinated fibre density and degeneration along with regeneration of unmyelinated fibres.[94] Quantitative studies have demonstrated degenerative or dystrophic changes in axonal and dendritic components of sympathetic ganglia in the absence of significant neuron loss, as well as alterations in the postganglionic autonomic innervation of various end organs.[95]

Nerve Vasculature

Structural abnormalities of the vessels supplying the peripheral nerve include arteriolar attenuation, venous distention, arteriovenous shunting, and new vessel formation[96,97] along with intimal hyperplasia, hypertrophy[98] and denervation.[99]

MEASURES OF NEUROPATHY

The diagnosis and staging of neuropathy are important not only for day-to-day clinical practice, but also for the conduct of clinical protocols to assess its aetiology and natural history and to test new proposed treatments.

Clinical Symptoms

Accurate recording of symptoms is essential both for clinical practice and trials of new medications. The **neuropathy symptom score**

(NSS) is a standardized list of questions and neuropathic symptoms that is applied by a trained individual in a standardized manner. A simplified NSS has been used for epidemiologic studies and can be applied in clinical practice.[22,27,50,100]

Table- 5[101]

Diabetic Neuropathy symptom score:
1 point for each positive response
Unsteadiness of gait
Pain/burning/aching of feet
Prickling sensation of feet/legs
Numbness feet

Clinical Signs

For assessing clinical signs, two simple instruments can be used in clinical practice, First[102] the Michigan Neuropathy Screening Instrument (MNSI); this two-step program is used for diagnosis and staging of neuropathy. The MNSI consists of a 15-question yes/no symptom questionnaire that is supplemented by a simple clinical examination. Patients with an abnormal score on the MNSI are then referred for QSTs and EP. Second, the simplified neuropathy disability score (NDS) [103] is a simple clinical examination that sums abnormalities of reflexes and

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

• Are your feet numb • Burning pain • Feet sensitive to the touch • Able to sense feet when walking • Can you tell hot from cold water • Have you had an ulcer • Doctor-diagnosed neuropathy • Do you feel weak	• Symptoms worse at night • Do legs hurt when you walk • Prickling feeling • Muscle cramp • Bed covers hurt your skin • Does skin crack open • Have you had an amputation

sensory assessment; it has been used in clinical practice and epidemiologic studies.

Neurology Deficit Score[103] is calculated as follows:

Table- 6

Vibration perception
Temperature perception
Pin prick
Normal =0 Abnormal =1
Achilles Reflex - present =0,present with reinforcement=1 absent =2

Quantitative Sensory Testing

QST's assess the patient's ability to detect a number of sensory stimuli and have the advantage that they directly assess the degree of sensory loss at the most vulnerable site: the foot. Some of the more commonly used techniques are now briefly discussed.

Semmes-Weinstein Monofilaments

Semmes-Weinstein monofilaments comprise sets of nylon filaments of variable diameter that buckle at a predefined force when applied to the

testing site. They are widely used in clinical practice and are particularly helpful in the identification of subjects who are at risk of neuropathic foot ulceration. Inability to perceive pressure of a 10-g monofilament has been shown in prospective studies to predict risk of neuropathic ulceration.[104]

Vibration Perception

Vibration perception thresholds (VPTs) test large myelinated fibre function. VPT increases with age in normal individuals and also tends to be higher in the lower extremities. Vibration of increasing intensity is applied using a biothesiometer. An abnormal reading greater than 25 V has been associated with a high risk of foot ulceration [105,56].

Thermal and Cooling Thresholds

Warm and cold sensation is transmitted via small myelinated and unmyelinated fibres and can be assessed by using a number of devices. However, they remain the most variable of all QSTs.

Computer-Assisted Sensory Examination

This complex methodology is currently regarded as state of the art for clinical trials and is a computerized device that can measure touch-pressure, vibration, and warm-cold thresholds using a forced-choice algorithm.

Autonomic Function Testing

Cardiovascular autonomic dysfunction can be evaluated in detail by employing Ewing and Clarke's battery of five tests: (1) the average

inspiratory-expiratory heart rate difference with six deep breaths, (2) the Valsalva ratio, (3) the 30:15 ratio, (4) the diastolic blood pressure response to isometric exercise, and (5) the systolic blood pressure fall to standing[106,107,42,48].

Electrophysiology

Electrophysiological measures of nerve function have been the mainstay of objective assessment of presence and severity of peripheral nerve involvement in patients with diabetes. They are sensitive, specific and reproducible. Studies are typically performed in the upper limb and lower limb nerves[108]. The tests are usually done using surface electrodes[109]. The analysis of action potential relates to the total number of active fibres whereas conduction studies reflect the functional status of large myelinated sensory and motor nerve fibres. It is better at diagnosing large fibre deficits whereas small fibre neuropathy is poorly diagnosed.[109]

Skin Biopsy

Immunohistochemical quantification of Intraepidermal nerve fibres (IENF) using the panaxonal marker protein gene product 9.5 is now established as an early and sensitive marker of nerve damage in diabetic neuropathy. A significant loss of IENF has been demonstrated in patients with no neurological deficits and normal quantitative sensory testing as well as electrophysiology [110] and a reduction in IENF regenerative capacity

occurs in diabetic patients[111].These abnormalities are specifically seen in patients with painful diabetic neuropathy [112]. Patients with small fibre

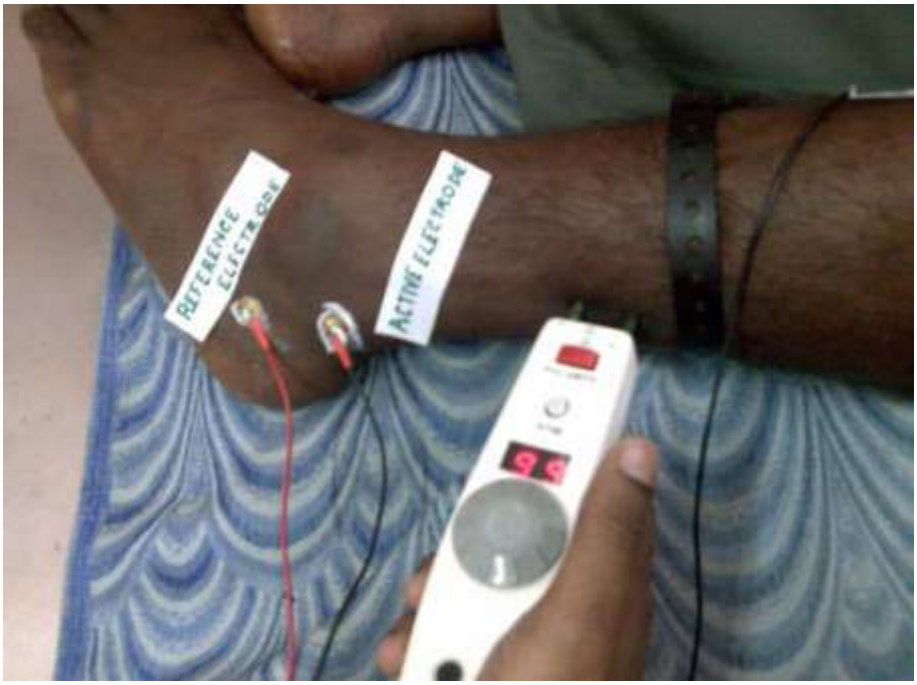
PERCEPTION OF PRESSURE USING SEMMES – WEINSTEIN MONOFILAMENTS

NERVE CONDUCTION STUDY MACHINE

COMMON PERONEAL NERVE STIMULATION AT ANKLE

COMMON PERONEAL NERVE STIMULATION AT KNEE

SURAL NERVE STIMULATION AT KNEE

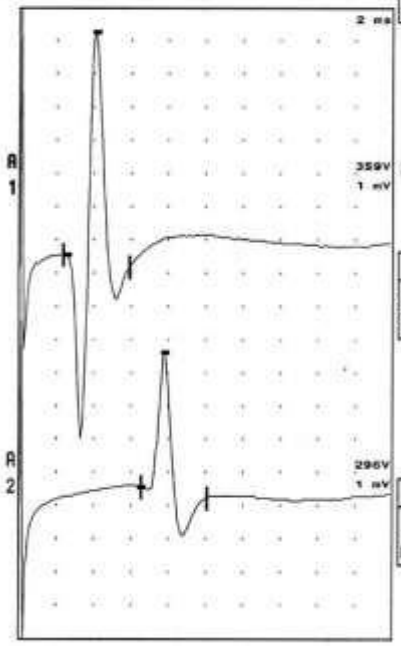


NERVE CONDUCTION STUDY REPORT

UTCVM Electrodiagnostic Laboratory

MNC Record # 1 Tibial nerve 12:06:29

Switch: N-R Stim: 1	Rate:Non-Recurrent	Level: 359 V	Dur: 0.1 ms	Single
		Step: 1	Average: Off	Rectify: Off



Recording Site :Abductor hallucis

STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms
A1: Ankle	6.5	3.5	4.078	4.105
A2: Pop. fossa	2.3	3.6	6.719	8.186

SEGMENT	DIST mm	DIFF ms	CV m/s
Ankle-Pop. fossa		4.2	80.6

neuropathy and impaired glucose tolerance demonstrate a significant loss of IENF which improves with no change in QST or neurophysiology, suggesting that the assessment of IENF may be a more sensitive marker of nerve repair following therapeutic intervention[113].

Corneal confocal microscopy

Corneal confocal microscopy represents a novel technique in vivo clinical examination - technique that is capable of imaging corneal nerve fibres. It has been shown to accurately define the extent of corneal nerve damage which has been related to the severity of somatic diabetic neuropathy[114,115]. It can detect small fibre neuropathy before there is decrease in nerve fibre density.[110]

TREATMENT

Therapies for diabetic neuropathy include those for symptomatic relief and those that may alter (slow) the progressive loss of nerve function that characterizes the natural history of neuropathy.

Sensory Neuropathy

Symptomatic relief -

- **Glycemic Control** : Of all the treatments, tight and stable glycemic control is probably the only one that may provide symptomatic relief as well as slow the relentless progression of neuropathy.[30] As it is probably blood glucose flux that induces neuropathic pain[56], stability rather than the actual level of glycemic control may be most

important in pain relief[116]. The method of achieving stable control does not seem to be critical; there is no evidence that insulin is superior if the blood glucose is well controlled by oral hypoglycaemic agents.

- Risk factors for neuropathy including hypertension and hyper triglyceridemia should be treated.
- Avoidance of neurotoxins like alcohol, smoking, and supplementation of vitamins for possible deficiencies of vitamin B12 and folate.
- **Tricyclic Antidepressants**: Until new therapies are proved to relieve symptoms in appropriately designed trials[117], the tricyclic antidepressant drugs, such as amitriptyline and imipramine, will remain useful first-line agents for painful neuropathy in developing countries. The main side effects are sedation and anticholinergic effects like constipation, dry mouth, weight gain and orthostatic hypotension. These side effects are particularly problematic in the elderly and in them it is advisable to start on a very small dose. The secondary amines nortriptyline and desipramine have a less troublesome side- effect profile[118].
- **Serotonin and noradrenaline reuptake inhibitors**: The serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine has both analgesic and antidepressant effects and can be used for the

treatment of diabetic peripheral neuropathic pain[119]. Unlike tricyclics, some anticonvulsants and opioids, it does not generally require dose titration.

- **Anticonvulsants**: Carbamazepine is used in the management of neuropathic pain; Gabapentin [120] is also another commonly used agent. It binds to δ2 subunit of calcium channels on neurons. It is not metabolised in the body and has no drug interactions. It has a low side effect profile. Pregabalin is the next preferred anticonvulsant used. The other anticonvulsants which may also be used include phenytoin, lamotrigine, topiramate and tiagabine.
- **Local anaesthetic antiarrythmics**—Intravenous lignocaine and its oral counterpart mexiletine are sodium channel antagonists which can be used for pain relief. They reduce the spontaneous abnormal and evoked discharges in damaged peripheral nerves thought to be responsible for pain generation. Both have been found to be efficacious.
- **Opiods** – May be tried in the treatment of neuropathic pain in patients who fail to respond to adjuvant analgesics. Drugs like tramadol, morphine, methadone, oxycodone and levorphanol can be used.
- **Topical agents** – Agents approved for use include caspsaicin, lignocaine.

- **Alternative therapies** - Transcutaneous electrical nerve stimulation, neuromuscular electrical stimulation, Interferential stimulation, Laser therapy, Electromagnetic field therapy, Acupuncture[121].

Potential Future therapies

- **Alpha - Lipoic Acid -**There is accumulating evidence to suggest that free radical–mediated oxidative stress is implicated in the pathogenesis of neuropathy. Alpha-lipoic acid, an antioxidant has been tried in clinical trials and has reported some benefit in symptoms and signs though without improvement in nerve conduction velocity[122]**.**
- **Aldose reductase inhibitors** – They reduce the flux of glucose through the polyol pathway (Tolrestat, Zenarestat & Zopolrestat). In a randomized, placebo controlled, double-blind, multiple-dose clinical trial with Zenarestat, dose-dependent increments in sural nerve sorbitol suppression were accompanied by significant improvement in NCV.[123].
- **γ linolenic acid**[124] – Essential fatty acid which is important constituent of neuronal membranes lipids and is a substrate for prostaglandin E formation which is important in maintaining nerve blood flow.
- **Aminogaunidine and its congeners** [125]- prevent formation of AGES

- **Protein Kinase C β inhibitors** – Protein kinase C activation is a critical step in the pathway to the diabetic complications. Intracellular hyperglycaemia increases diacylglycerol levels, which activates protein kinase C (PKC) formation, leading to multiple pathogenetic consequences, including altered expression of endothelial nitric oxide synthetase and VEGF, However, a large RCT failed to demonstrate any benefit of the drug over placebo in measures of nerve function[126].
- **Neurotropic factors** [127]– Decreased expression of nerve growth factors and its receptors reduce support of small unmyelinated neurons. Administration of recombinant nerve growth factors restores these levels to normal and decreases the manifestations of sensory neuropathy.
- **ACE inhibitors** – ACE inhibitors have been proposed to be useful. A preliminary controlled study of ACE inhibitors in early neuropathy confirmed a significant benefit over placebo in EP parameters[126].

Autonomic Neuropathy

- **Erectile Dysfunction** - Because autonomic neuropathy is one of several contributory causes in erectile dysfunction (ED), a multifaceted approach to management is indicated[128,129].

Psychosexual counselling and altering drug therapy to remove the factors associated with ED are beneficial in many cases[128]. Sildenafil, an orally active selective inhibitor of phosphodiesterase 5 (PDE-5), is efficacious for ED in diabetic males.

- **Sweating Disorders** - The first specific treatment for gustatory sweating has been reported. Glycopyrrolate is an antimuscarinic compound that, when applied topically to the affected area, results in a marked reduction of sweating while eating "trigger" foods. Its efficacy was confirmed in a randomized controlled trial[130].
- **Others**- Treatment of diabetic gastroparesis involves measures to enhance gastric motility and emptying. Metoclopramide, a dopamine antagonist, directly stimulates antral muscle and may also mediate acetylcholine release. Alternative agents include domperidone, or erythromycin, which directly stimulates motilin receptors. Constipation may be treated with a combination of prokinetic agents such as metoclopramide and cisapride.
- **Postural hypotension** may be treated with mineralocorticoids such as fludrocortisone, sympathomimetic agents, and dopamine blockers. Urinary bladder difficulties are addressed with regular voiding, self-catheterization, and cholinergic agonists such as bethanechol chloride, which stimulates muscarinic, postganglionic receptors, enhancing bladder motility and emptying [131].

- **Foot care** –Last but not the least. The feet should be examined everyday for bruises, cracks, dry skin, ingrown toenails, blisters or discolouration. Wash feet everyday using warm water and mild soap and apply moisturising cream to prevent the feet from being dry and developing cracks. Toe nails should be well maintained. Do not cut toe nails too short. The patients are advised to cut nails straight across and always check nails for sharp edges. Remove callus on a regular basis. Wear thick socks and well cushioned footwear which are big enough to cover both the feet and the sock.

The late sequelae of diabetic neuropathy are usually considered to be neuropathic foot ulceration, neuroarthropathy (Charcot's foot), and amputation.

Neuropathic Foot Ulceration

Distal sensory and sympathetic neuropathies are the most important component causes that lead to foot ulceration. However, the neuropathic foot does not spontaneously ulcerate; typically, it is the combination of neuropathy with other risk factors such as deformity and unperceived trauma that results in ulceration. International guidelines on the clinical

management of neuropathy, therefore, emphasize the importance of regular foot examinations and education in self-foot care in the management of neuropathy

Charcot's Neuroarthropathy

Charcot's neuroarthropathy is a less common but clinically important and potentially devastating disorder. Permissive features for the development of a Charcot's joint include peripheral sensorimotor neuropathy, sympathetic denervation in the foot, and intact peripheral circulation; minor, unperceived trauma is often the initiating event. It is believed that following repetitive minor trauma, osteoblastic activity is stimulated with remodelling of bone. A high index of suspicion must exist if a neuropathic patient has unilateral unexplained swelling and warmth in a foot, with the possibility of infection also being kept in mind. Contrary to earlier texts, discomfort may be experienced, although the patient is still usually able to walk. Detailed assessment and investigation of such a patient is essential, and rest or casting of a suspected Charcot's foot is usually recommended.

IGT and Neuropathy

IGT has come to be increasingly associated with microvascular complications contrary to the previous belief that it is associated with only arterial disease. Most patients with IGT and neuropathy have a symmetrical distal sensory neuropathy with prominent neuropathic pain as

well as autonomic disturbances [132]. Studies have shown that aggressive life style modification (diet and exercise) can reverse the low intraepidermal nerve fibre density as well as neuropathic symptoms [133].

MATERIALS AND METHODS

Place of study - Department of Medicine, Govt Kilpauk Medical College, Chennai 10

Collaborating department – Department of Diabetology, Kilpauk Medical College, Department of Neurology, Kilpauk Medical College.

Duration of study - November 2009 - October 2110.

Type of study - Cross sectional study

Study population – 40 patients were randomly selected in each of the three groups, namely newly diagnosed diabetes mellitus, impaired glucose tolerance and control from among patients attending the diabetic clinic, KMC

Materials - Detailed questionnaire, brief clinical examination (timed vibration, ankle reflex & perception of pain & temperature), BMI calculation, BP, GTT, FBS, PPBS, Nerve conduction study, HbA1c.

Inclusion criteria –

Newly diagnosed drug naive Type 2 diabetes mellitus patients.

Patients with impaired glucose tolerance.

Patients who are euglycemic without other risk factors.

Exclusion criteria –

Known type 2 diabetes mellitus

Chronic renal failure

Chronic alcoholics

Uncontrolled hypertension

Patients on ATT

Known carcinoma patients

Patients on drugs known to cause peripheral neuropathy.

Methodology -

- A detailed history was taken using a structured questionnaire.
- Demographic data: Patients name, age, address, occupation, and information regarding socioeconomic status (modified kuppuswamy scale of social classification [134]) was obtained.
- Also information regarding relevant past and family history was obtained.

❖ Clinical neuropathy was assessed using a questionnaire on neuropathic symptoms and it was analysed using diabetic neuropathy symptom score [101]. Neuropathic pain was described as pain in the extremities in the absence of history of trauma and any external factors. Paraesthesia was defined as sensation of burning, sharpness, tingling or numbness. A score of 1 or more than one was considered significant.

❖ **Body mass index (BMI**) is calculated with height and weight of the subject using the following formula.

BMI= weight (kg) / height (m) $^{2.}$ BMI was classified according to WHO criteria for Asian Population.[135]

Values: < 18.5 kg / m^2 was taken as underweight.

18.5 – 22.9 kg / m^2 was taken as normal weight

23- 29.9 kg / m^2 was taken as overweight.

> 30 kg/m^2 was taken as obesity

❖ **Blood pressure** – Right upper arm blood pressure is taken in supine position by using sphygmomanometer under appropriate conditions.

❖ **Clinical neuropathy** was assessed using a brief clinical examination. Timed Vibration(comparing patients' vibration sense with the examiner),pain and temperature sensation in the foot and the ankle jerk was examined. Findings of the examination was assessed using Neuropathy

Disability Score [103]. A score of 2 or more was considered to indicate neuropathy.

❖ Diabetes /Impaired glucose tolerance/ Normalcy was confirmed using FBS/PPBS/OGTT/HbA1c tests and interpreted using 2010 ADA criteria for the same.

The OGTT/Oral glucose tolerance test was done in the morning after 10-16 hours of overnight fast (water may be taken) following at least three days of unrestricted diet. Smoking and all physical activities were avoided. At the commencement of the test a fasting blood sample is drawn. The subject then drinks 75g of glucose in 250 -300 ml of water. A further blood sample is obtained after 2 hours. Both blood samples were collected in fluoride oxalate tubes which prevent the red blood cells from metabolising glucose.

Diabetes is diagnosed if the fasting value is ≥126 or the 2 hour plasma glucose is ≥ 200.

IGT is diagnosed if the 2 hour plasma glucose is ≥140 ≤199.

❖ HbA1c - Blood sample was collected in EDTA tubes and HbA1c was measured using HPLC method.

❖ Nerve conduction study: Nerve conduction study was done using MEDICAID electromyography machine using surface electrodes by standard procedure at room temperature by trained personnel. Motor nerve conduction velocity (MNCV) and compound muscle action potential

(CAMP) was measured in the leg segment (ankle to knee) of peroneal and tibial nerves on both sides. Also sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) was recorded for both sural nerves in the leg segment. The values considered abnormal were as follows:

Peroneal nerve – CMAP < 2mv, MNCV <42m/s

Tibial nerve - CMAP <3 mv, MNCV<41m/s

Sural nerve – SNAP < 6mv, SNCV <42m/s

For statistical analysis the more abnormal of the 2 values for each nerve were taken.

- The patient was diagnosed to have peripheral neuropathy if two of the three namely neuropathy symptom score, neuropathy disability score and nerve conduction study was abnormal (criteria by Rochester Diabetic Neuropathy study).
- **Statistical analysis** – The results were analysed using SPSS software.

The statistical tests of analysis used were

Chi square test – for analysing discrete variables.

Two sample 'T' test- for continuous variables (2 variables)

ANOVA test (Analysis of variance test) – for continuous variables (>2) variables.

Level of significance - p= 0.05.

RESULTS

The study sample included patients each in three groups,

- Group1- newly detected diabetes mellitus, n = 40
- Group2- impaired glucose tolerance, n = 40
- Group3- control, n = 40

Age distribution of cases in three groups

Table-7

Age group	Group 1	Group 2	Group 3
20-30	1	1	3
31-40	12	12	12
41-50	18	17	15
>51	9	10	10

p= 0.924, not significant,

There was no significant difference between the three groups with regard to age distribution

Sex distribution of patients

Table 8

Sex	Group 1	Group 2	Group 3
Male	18	16	19
Female	22	24	21

p= 0.904 not significant.

There was no significant difference between the three groups with regard to distribution of patients according to sex.

Distribution of patients according to socioeconomic status[134]

Table-9

Socioeconomic status	Group 1	Group 2	Group 3
Low	28	25	29
Medium	12	15	11

p= 0.606, not significant.

There was no significant difference between the three groups with regard to socioeconomic status.

Distribution of patients according to past history of hypertension

Table 10

Hypertensive	Group 1	Group 2	Group 3
Yes	3	7	3
No	37	33	37

p= 0.252, not significant

There was no significant difference between the three groups with regard to distribution of patients according to past history of hypertension.

None of the patients in the three groups had history of CAD/CVA/Renal disease**.**

Distribution of patients according to history of smoking.

Table 11

Smoking	Group 1	Group 2	Group 3
Yes	8	10	9
No	32	30	31

p= 0.866, not significant

There was no significant difference between the three groups with regard to the number of people having a history of smoking.

Distribution of patients according to Body Mass Index (BMI) [135]

(Table-12)

BMI(kg/m^2)	Group 1	Group 2	Group 3
<18.5	0	1	0
18.5 – 22.9	12	17	9
23 – 29.9	26	22	28
>30	2	0	3

p= 0.645, not significant

There was no significant difference between three groups with regard to BMI distribution.

Distribution of patients according to family history of diabetes mellitus

Table-13

Family history of diabetes mellitus	Group 1	Group 2	Group 3
Yes	16	18	8
No	24	22	32

P=.04, significant

There was a significant difference between the three groups with regard to family history of diabetes. Patients in the new diabetic as well as impaired glucose tolerance group has more number of patients having family history of diabetes compared with control group.

Distribution of patients according to neuropathy symptom score

(Table -14)

Neuropathy Symptom score	Group 1	Group 2	Group 3	Total
0	13 (32.5%)	23 (57.5%)	32 (80%)	68 (56.7%)
1	14 (35%)	9 (22.5%)	6 (15%)	29 (24.2%)
2	9 (22.5%)	7 (17.5%)	2 (5%)	18 (15%)
3	3 (7.5%)	1 (2.5%)	0 (0%)	4 (3.3%)
4	1 (2.5%)	0 (0%)	0 (0%)	1 (0.8%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100)

p= 0.007, Significant.

Significant symptom score (1 or more) was found in 67.5% (27) of new diabetics, in 42.5% (17) of IGT and in 20% of control group.

The number of patients with neuropathic symptoms was found to be significantly more in new diabetic as well as IGT group when compared to the control group.

Distribution of patients according to neuropathy disability score.

Table 15

Neurological Disability Score	Group 1	Group 2	Group 3	Total
0	26 (65%)	30 (75%)	35 (87.5%)	91 (75.8%)
1	7 (17.5%)	6 (15%)	5 (12.5%)	18 (15%)
2	5 (12.5%)	4 (10%)	0 (0%)	9 (7.5%)
3	2 (5%)	0 (0%)	0 (0%)	2 (1.7%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100%)

p = 0.111, not significant.

There was no significant difference in the distribution of patients according to neuropathy disability score in between the three groups.

Neuropathic disability score ≥ 2 was seen in 17.5% (7) of new diabetics, in 10% (4) of IGT and 0% in control group.

Motor nerve conduction abnormality distribution in the different study groups.

Table 16

Abnormality	Group 1	Group 2	Group 3	Total
Yes	15 (37.5%)	14 (35%)	1 (2.5%)	30 (25%)
No	25 (62.5%)	26 (65%)	39 (97.5%)	90 (75%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100%)

p= 0.000, significant

Abnormality in motor nerve conduction study was found in 37.5% of new diabetics, 35 % of patients with impaired glucose tolerance and in 2.5% of control population. The difference in distribution of cases with regard to motor nerve conduction abnormality between the three groups is statistically significant.

Sensory nerve conduction abnormalities in the three groups

Table 17

Abnormality	Group 1	Group 2	Group 3	Total
Yes	16 (40%)	12 (30%)	0 (0%)	28 (23.3%)
No	24 (60%)	28 (70%)	40 (100%)	92 (76.7%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100%)

p= 0.000, significant

Sensory nerve conduction abnormalities were found in 40% (16) of new diabetic group, in 30% (12) of IGT group and in 0% of control population. There was a significant difference in the distribution of patients in between the three groups with regard to sensory nerve conduction abnormality.

Prevalence of peripheral neuropathy[43] in the three groups.

Table 18

Neuropathy	Group 1	Group 2	Group 3	Total
Present	17 (42.5%)	8 (20%)	1 (2.5%)	26 (21.7%)
Absent	23 (57.5%)	32 (80%)	39 (97.5%)	94 (78.3%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100%)

p = 0.000 significant. The prevalence of peripheral neuropathy in this study was found to be 42.5% among the new diabetics, to be 20% among

the impaired glucose tolerant and 2.5% among the control population.

The difference in prevalence of peripheral neuropathy between the three groups was found to be statistically significant.

ANALYSIS OF RISK FACTORS

GROUP 1 – NEW DIABETICS

- **Age vs Neuropathy**

(Table 19)

Neuropathy	Age (yrs)		
	No . of. patients	Mean	SD
Present	17	46.41	9.805
Absent	23	43.57	7.867

p = 0.315, not significant. The mean age of patients with neuropathy was 46.42±9.8yrs compared to patients without neuropathy which is 43.57± 7.8yrs . There was no significant difference in the mean age among patients with and without neuropathy. Age is not associated with neuropathy.

❖ **Sex Vs neuropathy**

(Table 20)

Sex	Number of patients	Neuropathy		Total
		Present	absent	
Female		11	11	22
	% within neuropathy	64.7%	47.8%	
Male		6	12	18
	% within neuropathy	35.3%	52.2%	
Total		17	23	40
	% within neuropathy	100%	100%	

p= 0.289 not significant. 64.7% (11of 17) of the people with neuropathy were found to be females and 35.3% were (6 of 17) found to be males. The sex distribution difference of the two groups was not significant.

❖ **Socioeconomic status and neuropathy**

(Table 21)

Socioeconomic status	Number of patients	Neuropathy		Total
		Present	absent	
Lower		12	16	28
	% within neuropathy	70.6%	69.6%	
Middle		5	7	12
	% within neuropathy	29.4%	30.4%	
Total		17	23	40
	% within neuropathy	100%	100%	

p= 0.944, not significant. 70.6% (12 0f 17) patients with neuropathy belonged to lower socioeconomic status.

No association was found between neuropathy and socioeconomic status

There was no significant difference in the distribution of patients according to socioeconomic status among patients with neuropathy when compared to patients without neuropathy.

❖ **Smoking Vs neuropathy**

Table-22

Personal History - Smoking	Number of patients	Neuropathy		Total
		Present	Absent	
Yes		5	3	8
	% within neuropathy	29.4%	13%	
No		12	20	32
	% within neuropathy	70.6%%	87%	
Total		17	23	40
	% within neuropathy	100%	100%	

p= 0.201, not significant. Among the patients with neuropathy 29.4% (5 of 17) were found to be smokers. There was no significant difference between the groups with regard to history of smoking.

❖ **Family history of diabetes Vs neuropathy**

Table 23

Family History – Diabetes Mellitus	Number of patients	Neuropathy		Total
		Present	Absent	
Yes		9	7	16
	% within neuropathy	52.9%	30.4%	
No		8	16	24
	% within neuropathy	47.1%	69.6%	
Total		17	23	40
	% within neuropathy	100%	100%	

p= 0.151, not significant. There was no association found between family history of diabetes and neuropathy. 9 of 17 (52.9%) patients with neuropathy had family history of diabetes as against 7 of 23 without neuropathy. This difference was statistically not significant.

❖ **BMI Vs Neuropathy**

(Table 24)

Neuropathy	BMI(kg/m^2)		
	No .of.patients	Mean	SD
Present	17	26.65	2.737
Absent	23	22.91	2.295

p= 0.000 significant. The mean BMI of patients with neuropathy was 26 ± 2.7 when compared to patients without neuropathy which was found to be

22.91 ± 2.2 and the difference is significant. BMI was found to be strongly associated with neuropathy.

❖ **Blood pressure Vs Neuropathy**

Table 25

	Neuropathy	Number of patients	Mean	SD
Systolic BP	**Present**	17	137.29	17.930
	Absent	23	126.52	12.391
Diastolic BP	**Present**	17	84.71	11.661
	Absent	23	77.04	8.798

BP Systolic- p= 0.030 significant, BP Diastolic p= 0.023, significant

A significant association was found between both systolic and diastolic Blood Pressure and neuropathy.

The mean systolic BP of patients with neuropathy was 137±17mm of Hg compared to 126.52±12 among patients without neuropathy.

The mean diastolic BP in patients with neuropathy was found to be 84.7±11 when compared to 77.04±8.7 in patients without neuropathy.

❖ **FBS/PPBS/HbA1c Vs Neuropathy**

Table 26

	Neuropathy	Number of patients	Mean	SD
FBS	**Present**	17	144.94	21.058
	Absent	23	137.04	17.057
PPBS	**Present**	17	297.88	52.003
	Absent	23	254.74	44.518
HbA1c	**Present**	17	10.85	1.577
	Absent	23	8.52	1.230

FBS; p= 0.198 not significant, PPBS; p= 0.008 Significant,

HbA1c; p= 0.000 Significant.

The mean FBS of patients with neuropathy was 144.9 ± 21.08mg/dl, whereas it was 137.04mg/dl among patients without neuropathy.

The mean PPBS of patients with neuropathy was 297.88mg/dl whereas the mean PPBS of patients without neuropathy was 254.74mg/dl.

The mean HbA1c of patients with neuropathy was 10.85 when compared to 8.52 among patients without neuropathy.

A significant association was found between post prandial blood sugar values and HbA1c with neuropathy in new diabetics. No significant association was found between fasting blood sugar values and neuropathy.

GROUP 2 – IMPAIRED GLUCOSE TOLERANCE

- **Age Vs Neuropathy**

Table 27

Neuropathy	Age (yrs)		
	No .of. patients	Mean	SD
Present	8	55.00	7.964
Absent	32	42.50	6.965

p= 0.000 Significant.

The mean age of patients with neuropathy was found to be 55 ± 7.9yrs when compared to patients without neuropathy which was 42.50 ± 6.9yrs. The difference in the mean age between the two groups was found to be statistically significant. Age was found to be associated with neuropathy in patients with impaired glucose tolerance.

- **Sex Vs Neuropathy**

Table 28

Sex	Number of patients	Neuropathy		Total
		Present	Absent	
Female		3	20	23
	% within neuropathy	37.5%	62.5%	
Male		5	12	17
	% within neuropathy	62.5%	37.5%	
total		8	32	40
	% within neuropathy	100%	100%	

p= 0.201 not significant. 5(62.5%) patients among the 8 patients who had neuropathy were males where as females constituted 37.5% (3/8). This distribution not found to be significant when compared with patients without neuropathy.

❖ **Socioeconomic status and neuropathy.**

Table 29

Socioeconomic status	Number of patients	Neuropathy		Total
		Present	Absent	
Lower		6	19	25
	% within neuropathy	75%	59.4%	
Middle		2	13	15
	% within neuropathy	25%	40.6%	
total		8	32	40
	% within neuropathy	100%	100%	

p= 0.414, not significant. 75% (6 of 8) patients with neuropathy were from the low socioeconomic status.

No association was found between neuropathy and socioeconomic status.

There is no significant difference in the distribution of patients according to socioeconomic status among patients with neuropathy when compared to patients without neuropathy

❖ **Smoking Vs Neuropathy**

Table 30

Personal History - Smoking	Number of patients	Neuropathy		Total
		Present	Absent	
Yes		3	7	10
	% within neuropathy	37.5%	21.9%	
No		5	25	30
	% within neuropathy	62.5%	78.1%	
Total		8	32	40
	% within neuropathy	100%	100%	

p= 0.361, not significant. 3 patients (37.5%) among patients with neuropathy (8) were smokers. The difference between the two groups was not found to be statistically significant. No association was found between smoking and neuropathy.

❖ **BMI Vs Neuropathy**

Table 31

Neuropathy	BMI(kg/m^2)		
	No .of.patients	Mean	SD
Present	8	25.88	2.031
Absent	32	22.44	2.435

p = 0.001, significant. The mean BMI of patients with neuropathy was found to be 25.88±2.031 when compared to patients without neuropathy which was 22.44±2.43 .The difference in the mean BMI between the two

groups was found to be statistically significant. BMI was found to be strongly associated with neuropathy.

❖ **Family history of diabetes and neuropathy**

Table 32

Family History – Diabetes Mellitus	Number of patients	Neuropathy		Total
		Present	Absent	
Yes		4	14	18
	% within neuropathy	50%	43.7%	
No		4	18	22
	% within neuropathy	50%	56.3%	
Total		8	32	40
	% within neuropathy	100%	100%	

p= 0.751, not significant.

50% (4 of 8) of patients with neuropathy had history of diabetes mellitus. Family history of diabetes was not found to be associated with diabetes mellitus.

❖ **Blood Pressure Vs neuropathy**

Table 33

	Neuropathy	Number of patients	Mean	SD
Systolic BP	**Present**	8	137.75	12.981
	Absent	32	124.25	15.581
Diastolic BP	**Present**	8	87.75	7.667
	Absent	32	77.94	9.374

p= 0.030, Systolic BP. p= 0.009, Diastolic BP. - Significant

The mean systolic BP found among patients with neuropathy was significantly higher than patients without neuropathy.137.75 vs 124.25.

The mean diastolic BP among patients with neuropathy was found to be significantly higher than patients without neuropathy (87.75 vs 77.94).

Both Systolic and Diastolic blood pressure was significantly associated with neuropathy

- **FBS/PPBS/HbA1c Vs Neuropathy**

Table 34

	Neuropathy	Number of patients	Mean	SD
FBS	**Present**	8	87.13	8.043
	Absent	32	79.22	8.257
PPBS	**Present**	8	182.25	9.020
	Absent	32	164.63	10.317
HbA1c	**Present**	8	6.24	0.106
	Absent	32	5.35	0.436

FBS: p=0.020, PPBS: p= 0.000, HbA1c: p= 0.000, Significant.

The mean FBS of patients with neuropathy (87.13) was significantly higher than patients without neuropathy (79.22).

The mean PPBS of patients with neuropathy was 182.25 which is significantly higher than patients without neuropathy (164.63).

The mean HbA1c of patients with neuropathy was significantly higher than patients without neuropathy (6.24 vs 5.35).

DISCUSSION

The prevalence of diabetic peripheral neuropathy according to the available literature varies from 8-43% in different populations. Partenan et al reported a prevalence of 8.3% among the newly diagnosed diabetic patients in his study which was conducted in Finland [47]. The UKPDS study which has been a landmark study in diabetes has shown a prevalence of 13% [30]. Richelle. J. Koopman found in her study a prevalence of 21.5% among U.S. adults [136]. Arindam dutta found a prevalence of 29% among the patients conducted in Manipur[137]. .Pradeepa and M. Rema et al in their Chennai Urban Rural Epidemiology study (CURES 55) found a prevalence of 19.5% among patients attending their outpatient clinic [52].The prevalence found in this study among patients attending our diabetology clinic in K.M.C was found to be 42.5%.

The higher prevalence obtained in my study population may be because of the small study group as well as due to the inclusion of electrophysiological tests in the diagnosis of neuropathy. Most population based studies mainly rely on NSS and biothesiometry. There is a lack of uniformity among studies regarding the criteria for diagnosis, characteristics of study populations, patient selection, criteria for diagnosis of diabetes and sensitivity of methods used to diagnose diabetic neuropathy. However it clearly indicates that peripheral neuropathy is

present in a significant percentage of diabetic people at time of diagnosis. Hence all people should be screened for peripheral neuropathy at diagnosis for optimal intervention.

Only two population based studies has evaluated the prevalence of peripheral neuropathy in IGT. First is the San Luis Valley study which had noted a prevalence of 11.2% for neuropathy among IGT and only 3.9% of normal subjects[49]. The[7] MONICA/KORA Augsburg surveys conducted in Germany have noted a prevalence of 13% in the IGT group compared to 7.3% among normal people [138]. The studies reported from India have been mainly on the nerve conduction abnormalities in impaired glucose tolerance. However Ericsson et al[139] and Sorensko JM, Kato M et al [140]in their studies found no association with neuropathy and IGT. Studies from India are lacking regarding the prevalence of neuropathy in impaired glucose tolerance. Vishwanathan et al has studied the nerve conduction abnormalities in different stages of glucose intolerance and has found that the mean MCV of impaired glucose tolerance patients were significantly lower than normal individuals [141]. Sevki Sahin et al have found a prevalence of 16% for neuropathy among patients with impaired glucose tolerance in his study which was done in Turkey [142].

In our study we have found a prevalence of 20% among the IGT group. This is a major finding and points towards the need for detailed

assessment of patients with impaired glucose tolerance on presentation. Also it shows the need for longitudinal studies in further evaluation of patients with impaired glucose tolerance

Symptoms of neuropathy were found in 67.5% of new diabetics, in 42.5% of IGT and in 20% of control group.

Arindham Dutta et al found in his study that 32% had symptoms of neuropathy among newly diagnosed diabetics, J.M. Lehtinen, M Uustitupa et al found neuropathic symptoms in 1.5% of his study group [143].Zsuzsanna Putz M.D et al found neuropathic symptoms in 12.19% patients in their study on IGT patients[144].

Neuropathic signs were found in 17.5% of new diabetics, in 10% of IGT and 0% in control group.

Arindam Dutta et al found 30% of his study group having neuropathic signs. J.M Lehtinen et al found neuropathic signs in 2.3% of patients, Klaus.P.Ratzmann found loss of reflexes in 13.6% of patients in his study [46]. Zsuzsanna Putz M.D et al found a prevalence of impaired sensation in 12.5% of patients in her study on IGT patients.

Abnormality in motor nerve conduction study was found in 37.5% of new diabetics, 35 % of patients with impaired glucose tolerance and in 2.5% of control population

Arindam Dutta et al found the prevalence of motor nerve conduction abnormality in his study in new diabetics to be 27%. Klaus .P.Ratzmann in his study found that the prevalence of motor nerve conduction abnormality was 15.7% among newly diagnosed diabetics.

Eugenia Rota et al found in her study that motor nerve involvement was present in 60% of patients who were new diabetics[145].Sevki Sahin et al found in their study on the nerve conduction abnormalities in IGT that motor nerve conduction abnormalities were found in 39.5% of patients.

Sensory nerve conduction abnormalities were found in 40% of new diabetic group, in 30% of IGT group and in 0% of control population.

Eugenia Rota et al found the prevalence of sensory nerve abnormalities to be 56.4% among newly diagnosed diabetics. Sevki Sahin et al in their study found sensory nerve conduction abnormalities were found in 21% patients.

RISK FACTOR ANALYSIS.

Group 1 – NEW DIABETICS

Age and Neuropathy- The mean age of patients with neuropathy (46.4yrs), though was higher when compared with patients without neuropathy (43.57yrs) it was not statistically significant.

J M Lehtinen et al and Solomon O.Ugoya [146] et al found in their studies that age was not associated with neuropathy. However studies by Arindham Dutta et al and Young et al[50] have shown significant association of age with neuropathy.

Sex and Neuropathy - This study has not found association between either sex and neuropathy. Studies by Solomon et al and Arindham Dutta et al [3] have also not found association between neuropathy and sex.

Socioeconomic status and neuropathy - There was no significant association between socioeconomic status and neuropathy.

Maria Eugenia Nina Mantilla has however found association with low socioeconomic status with neuropathy in their study among patients with diabetic neuropathy [147].

Smoking and Neuropathy - Smoking was not found to be associated with prevalence of neuropathy among new diabetics. Partenan et al, J.M Lehtinen et al found no association with smoking in their study. However the findings by M.L Sands et al of the San Luis Valley study found association between current smoking and neuropathy [148].

Family History of diabetes and Neuropathy - No association was found between family history of diabetes and prevalence of neuropathy in this

study. Similar observation was made in the studies done by Solomon O Ugoya et al and M L Sands et al in their studies.

BMI and Neuropathy - The mean BMI of patients with neuropathy (26.65) was found to be significantly higher than the patients without neuropathy (22.91).

This is in agreement with the findings of J.M.Lehtinen et al, Cohen A et al [149] and Arindham dutta et al in their studies. However the association was not found to be there in the CURES-55 study done by R. Pradeepa, M. Hema et al.

Blood Pressure and neuropathy – Both systolic and diastolic BP is found to be associated with neuropathy in this study.

Arindham Dutta et al found in their study that systolic and diastolic BP was higher in the neuropathy group but not statistically significant. Association of BP with neuropathy was found in studies done by Cohen et al, and Solomon O Ugoya in their studies.

Fasting and Post prandial blood sugars and neuropathy - Though the mean fasting as well post prandial blood sugar values were higher among patients with neuropathy statistically significant association was found only between post prandial blood sugars and neuropathy. Similar findings were

obtained by Ashok et al [150], Young et al, Arindham dutta et al and Junani Partenan et al in their studies.

HbA1c and Neuropathy – HbA1c was found to be strongly associated with neuropathy among the new diabetics. Similar findings were obtained by J.Partenan et al, R.Predeepa et al, Solomon O Ugoya, Cohen A et al and M.L Sands et al.

Group -2, IMPAIRED GLUCOSE TOLERANCE

Age and Neuropathy- The mean age of patients with IGT were found to be significantly higher than the patients without neuropathy.

Similar findings were obtained in the San Luis Valley studies and in the MONICA/KORA Augsburg studies.

Sex and neuropathy -No association was found between either sex, and neuropathy.

Vishawanathan et al has found in his study that male gender and nerve conduction abnormalities were related. San Luis Valley study also found that male gender and neuropathy were related.

Socioeconomic status and neuropathy -No association was found between socioeconomic status and neuropathy.

Family history of diabetes mellitus and neuropathy

There was no association found between family history of diabetes and neuropathy.

Smoking and Neuropathy - Singleton J.Robinson[64] in their studies have found that neuropathy of impaired glucose tolerance and smoking were not related. No association was found between smoking and neuropathy in the group of patients with impaired glucose tolerance with regard to neuropathy in this study.

BMI and neuropathy -The mean BMI of people with IGT and neuropathy was significantly higher than patients without neuropathy suggesting that BMI is associated with neuropathy in this group of patients.

San Luis Valley Study however did not find any association between BMI and neuropathy. Vishwananthan et al also found that there was no association between BMI and nerve conduction abnormalities. The MONICA/KORA Augsburg studies found that the BMI was not associated with neuropathy.

Blood Pressure and neuropathy – Both systolic and diastolic BP was found to be associated with neuropathy among patients with impaired glucose tolerance.

Vishwanathan et al found in their study that only systolic BP was associated with nerve conduction abnormalities.

FBS/PPBS/HbA1c

Neuropathy was found to be associated with all the glycemic parameters namely fasting blood sugar values, post prandial blood sugar values as well as HbA1c.

Vishwananthan et al have found a significant association between nerve conduction abnormalities and blood sugar values in their study. Similar results were also found in the San Luis valley Study.

This study clearly shows that there is a significant prevalence of neuropathy in patients at time of diagnosis of neuropathy and even more importantly there is significant prevalence among patients with IGT. This suggests that neuropathy emerges very early in the natural history of diabetic patients, perhaps modulated further by the influence of genetic and environmental factors. The increased prevalence in both groups as well as association with blood sugar values and HbA1c suggest that hyperglycaemia is an important trigger to the cascade of events culminating in neuropathy.

The role for other factors has to be further investigated as in most cases the available data is divided in its results. This study shows the need

for more longitudinal and population based studies in diabetes and especially in impaired glucose tolerance to further clarify the increased prevalence of neuropathy and find the risk factors associated with it. **ADA recommends that all patients with diabetes should be screened at diagnosis for the presence of neuropathy** and also given advice regarding foot care. **The increased prevalence in the impaired glucose tolerance group calls for early screening of these patients for neuropathy and initiate aggressive life style modifications** in these patients as it has shown not only improve but reverse neuropathic changes in these people. If patients can be identified in their stage of impaired glucose tolerance and if screened and treated for complications , then the morbidity associated with diabetes can be remarkably reduced. We can ensure that diabetic patients have fitter, happier lives rather than painful deformed lives.

This was a preliminary cross sectional study done to find the prevalence and risk factors of neuropathy in patients with diabetes and impaired glucose tolerance. The limitations of this study are that the study group was small and that the other risk factors for neuropathy like vitamin B12, hypothyroidism etc has not been ruled out in the study population. The increased prevalence of neuropathy in impaired glucose tolerance needs to be confirmed by a prospective long term study involving a large cohort of patients.

SUMMARY

- The aim of the present study was to find the prevalence of peripheral neuropathy in patients with newly diagnosed diabetes mellitus and in impaired glucose tolerance.
- Forty patients were selected in each of the three groups randomly from among patients attending the department of diabtology. The presence of neuropathy was assessed with the help of nerve conduction studies as well as symptoms and signs for the same. The patients were also assessed regarding the various risk factors that might be associated with the disease.
- The prevalence of diabetic neuropathy was found to be 42.5% among newly diagnosed diabetics and 20% among patients with impaired glucose tolerance.
- The risk factors found to be associated with neuropathy among new diabetics were BMI, blood pressure (both systolic and diastolic), postprandial blood sugar levels as well as HbA1c.
- The risk factors associated with the neuropathy of impaired glucose tolerance were age, BMI, systolic blood pressure, fasting and postprandial blood sugar values as well as HbA1c values.
- This study calls for early screening of newly diagnosed and impaired glucose tolerance patients for the presence of peripheral neuropathy.

CONCLUSION

- This study finds a significant prevalence of diabetic peripheral neuropathy in patients with newly detected diabetes mellitus and impaired glucose tolerance.
- This study finds the association of other components of metabolic syndrome namely hypertension and BMI with neuropathy in both the study groups. This indicates that in these patients a multifaceted treatment approach giving equal weightage to drug therapy as well as life style modification should be advocated.
- The study also highlights the importance of early screening of all patients with diabetes mellitus and even those in the stage of impaired glucose tolerance for complications, so that measures may be instituted to prevent and halt the progression of complications of diabetes mellitus.
- Effective measures to control the risk factors and early detection of diabetic neuropathy to prevent it from progressing are the key to maintain the quality of life in the diabetic population. This not only decreases the morbidity and mortality among the diabetic patients but also lessen the enormous financial burden faced while treating such complications, in the developing countries like India.

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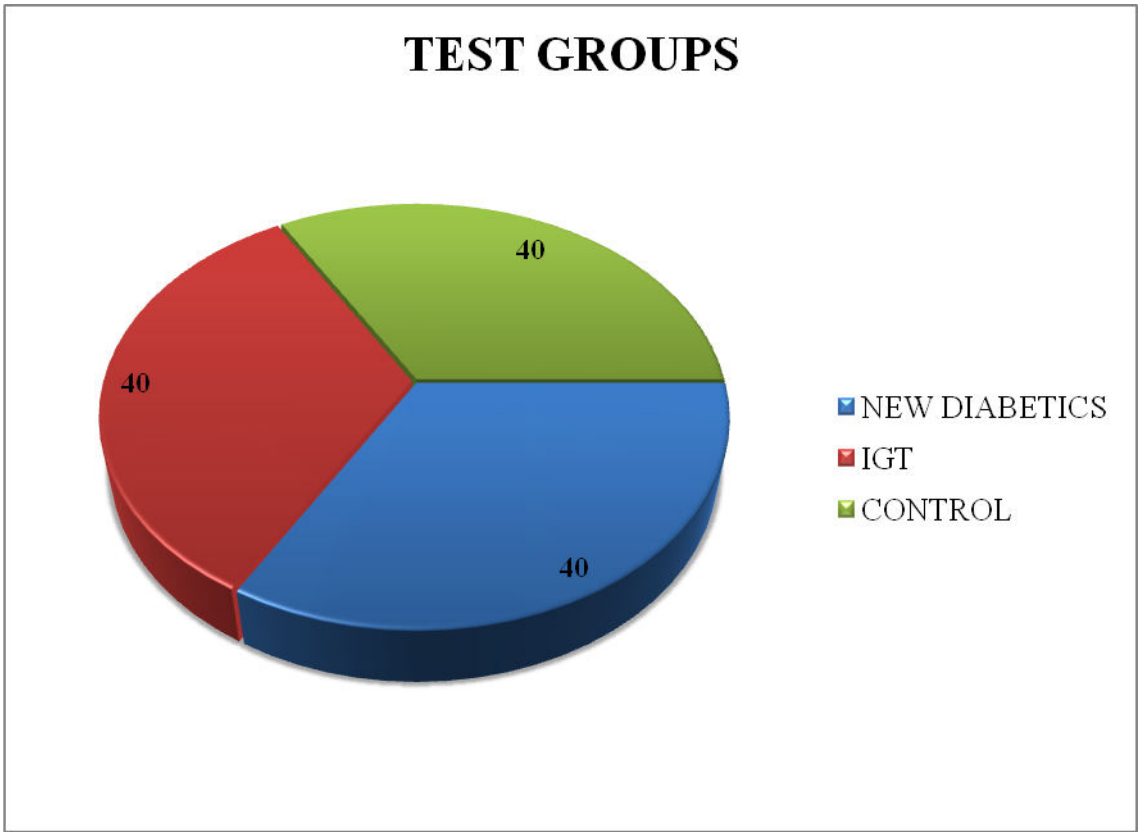
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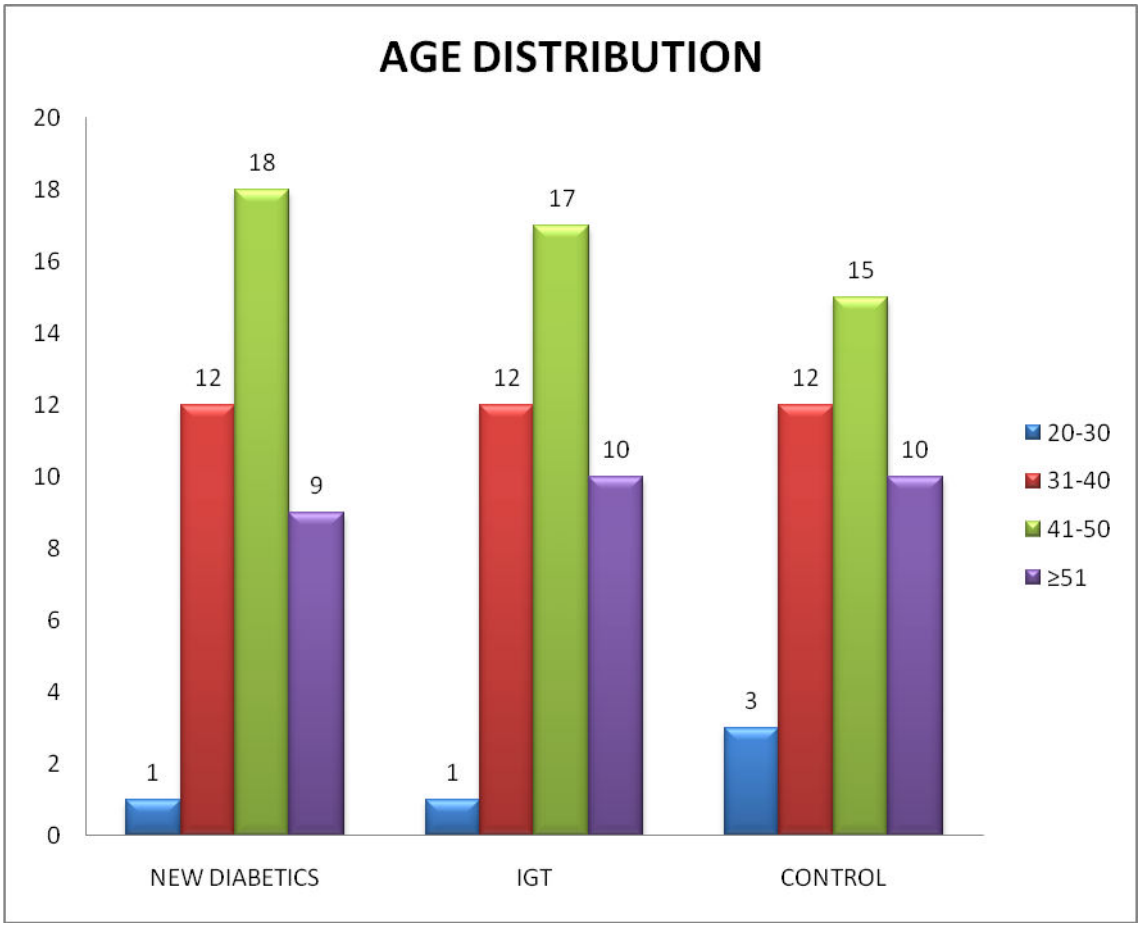
CONTROL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CONTROL
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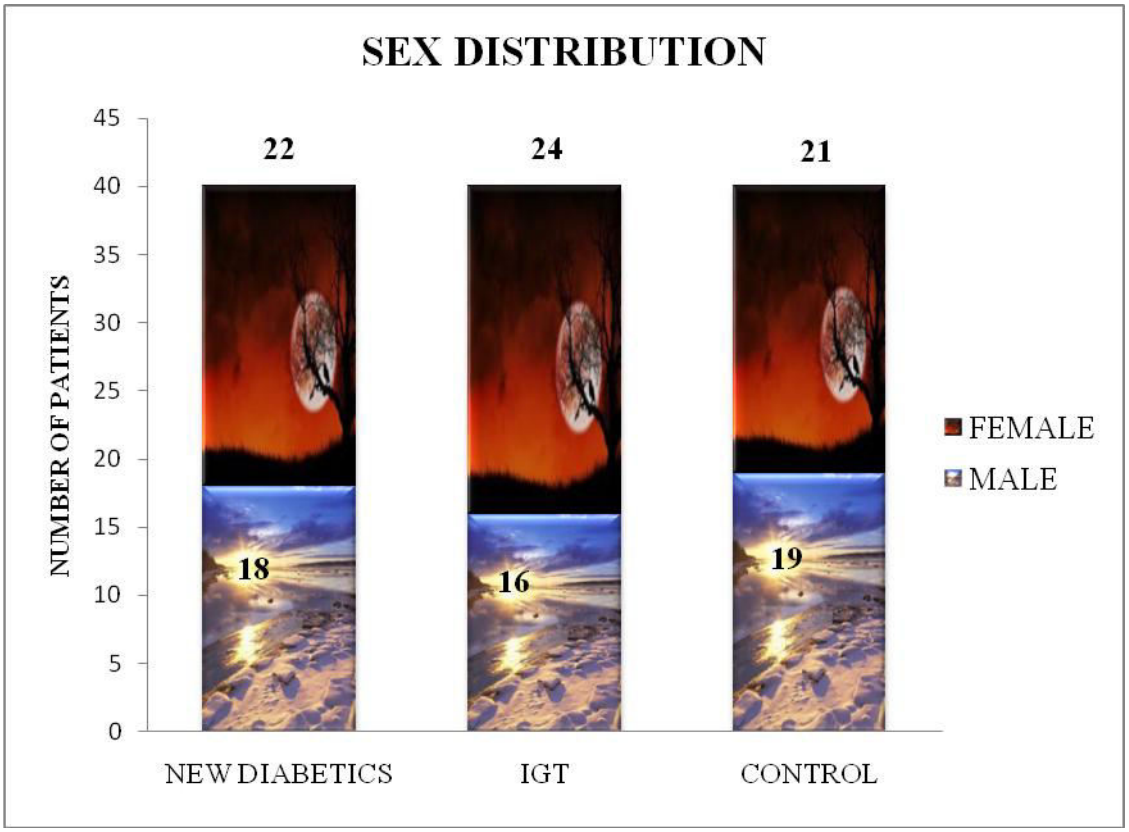
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NUMBER OF PATIENTS
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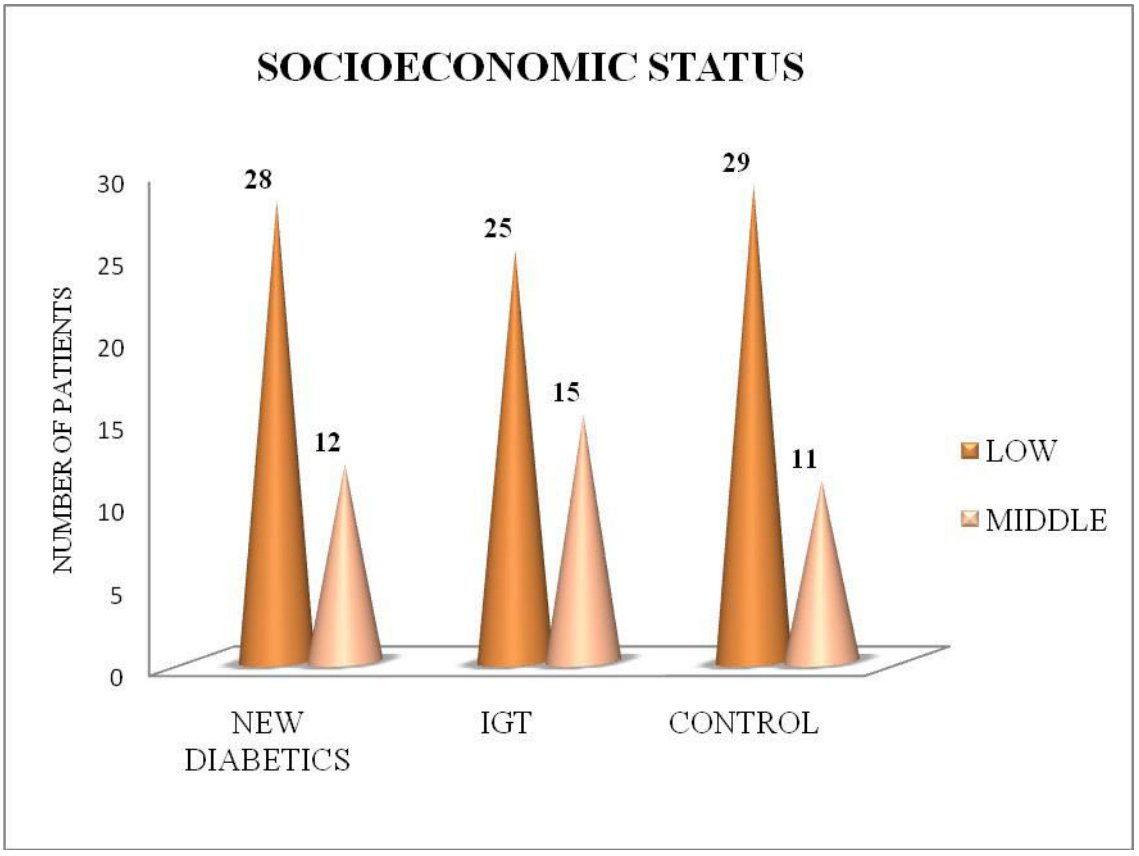
FEMALE
MALE
NEW DIABETICS
IGT
CONTROL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NUMBER OF PATIENTS
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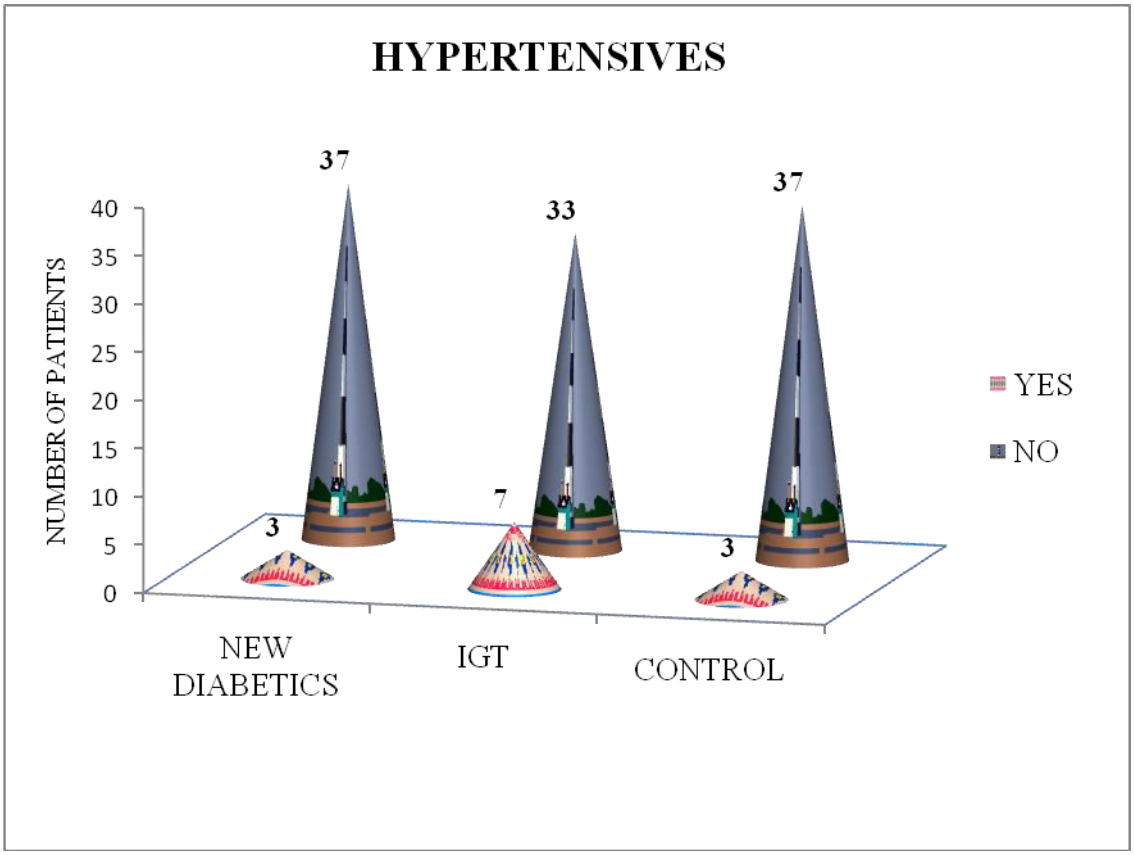
MIDDLE
NEW DIABETICS
IGT
CONTROL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NUMBER OF PATIENTS
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NEW DIABETICS
IGT
CONTROL
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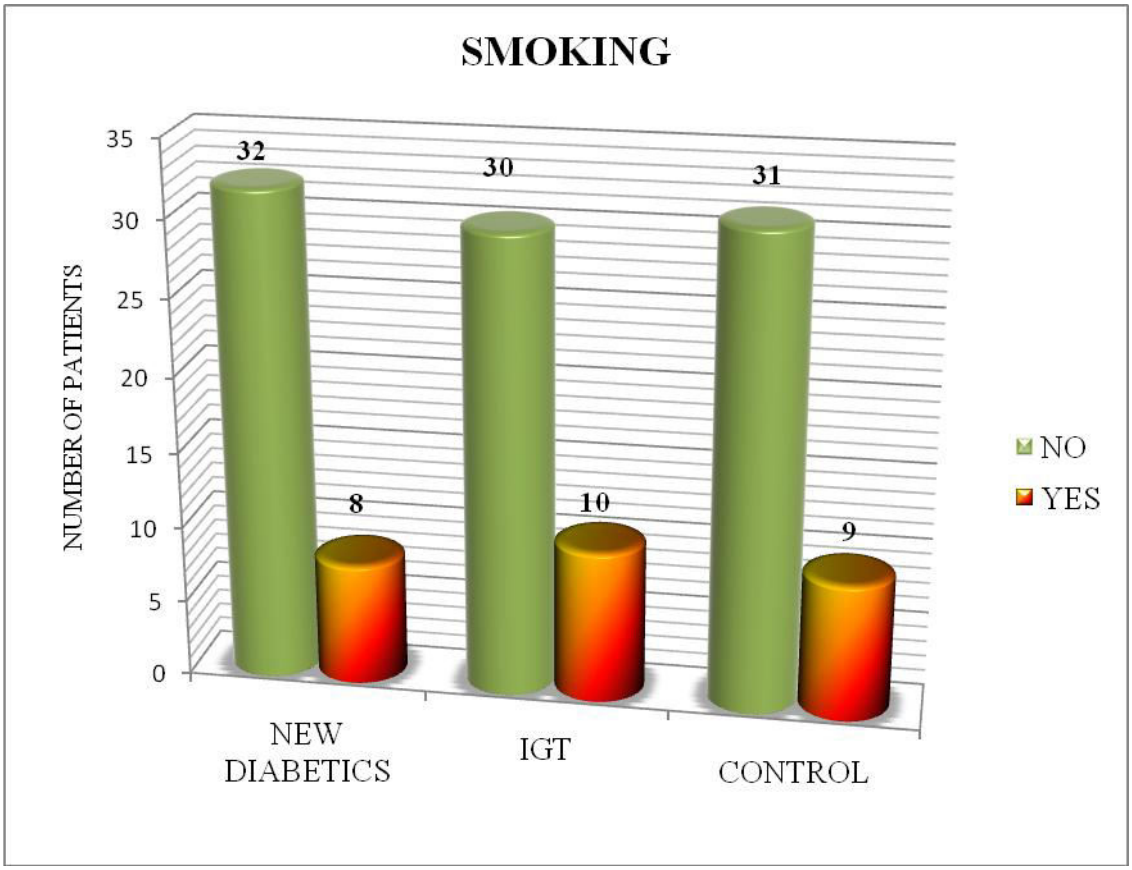
NO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NUMBER OF PATIENTS
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NEW DIABETICS
IGT
CONTROL
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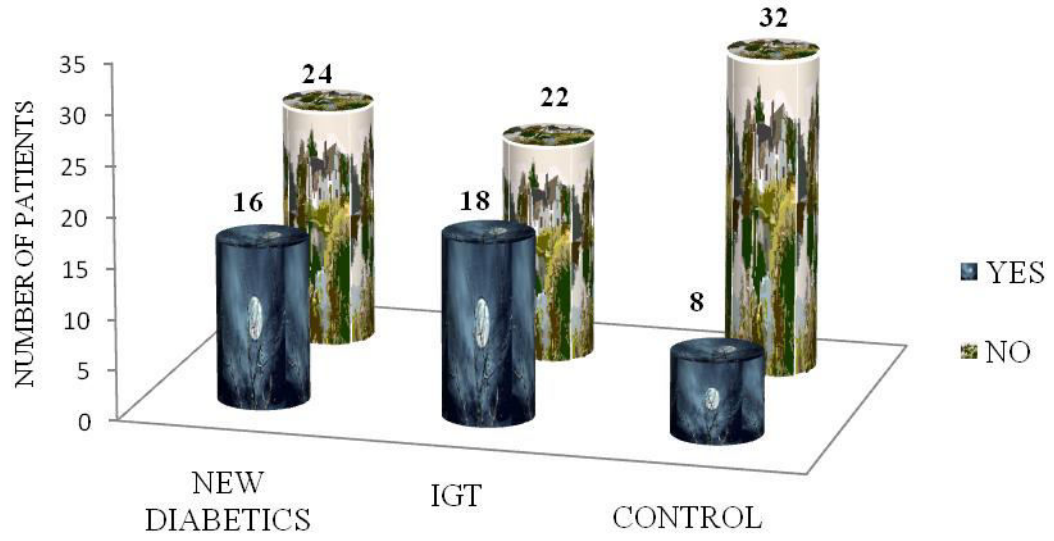
YES

FAMILY HISTORY OF DIABETES MELLITUS



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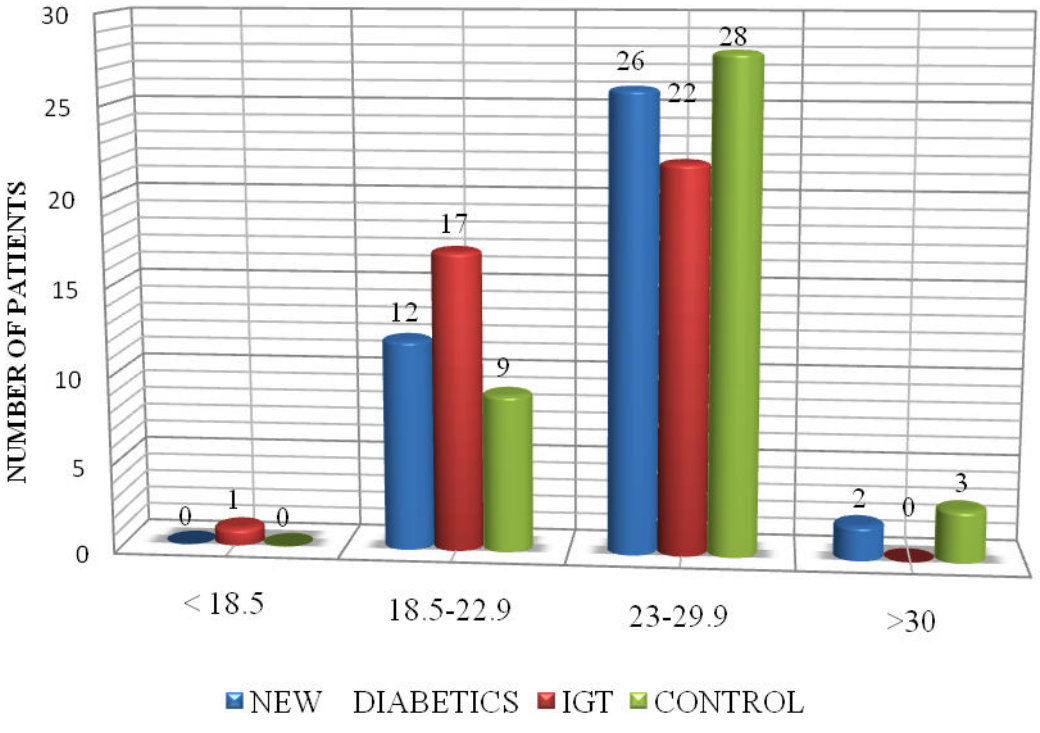

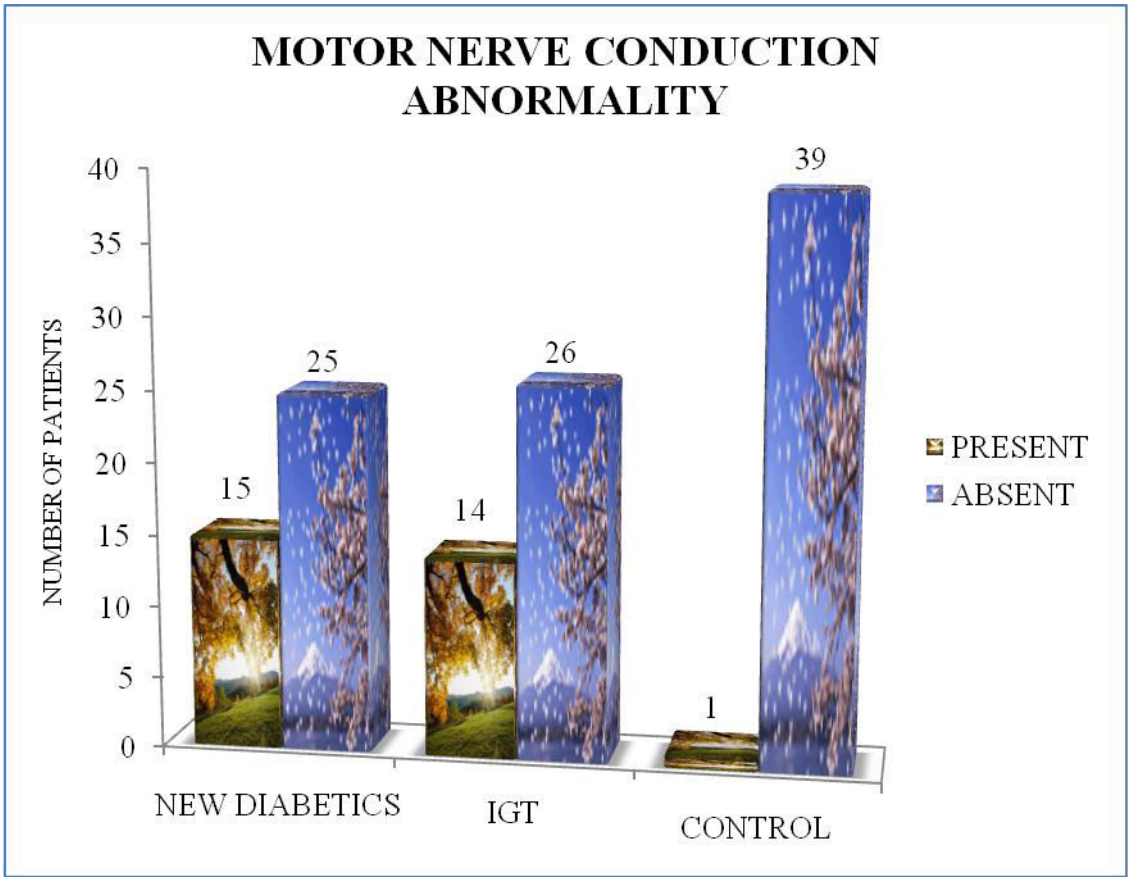
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NEW DIABETICS
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PRESENT
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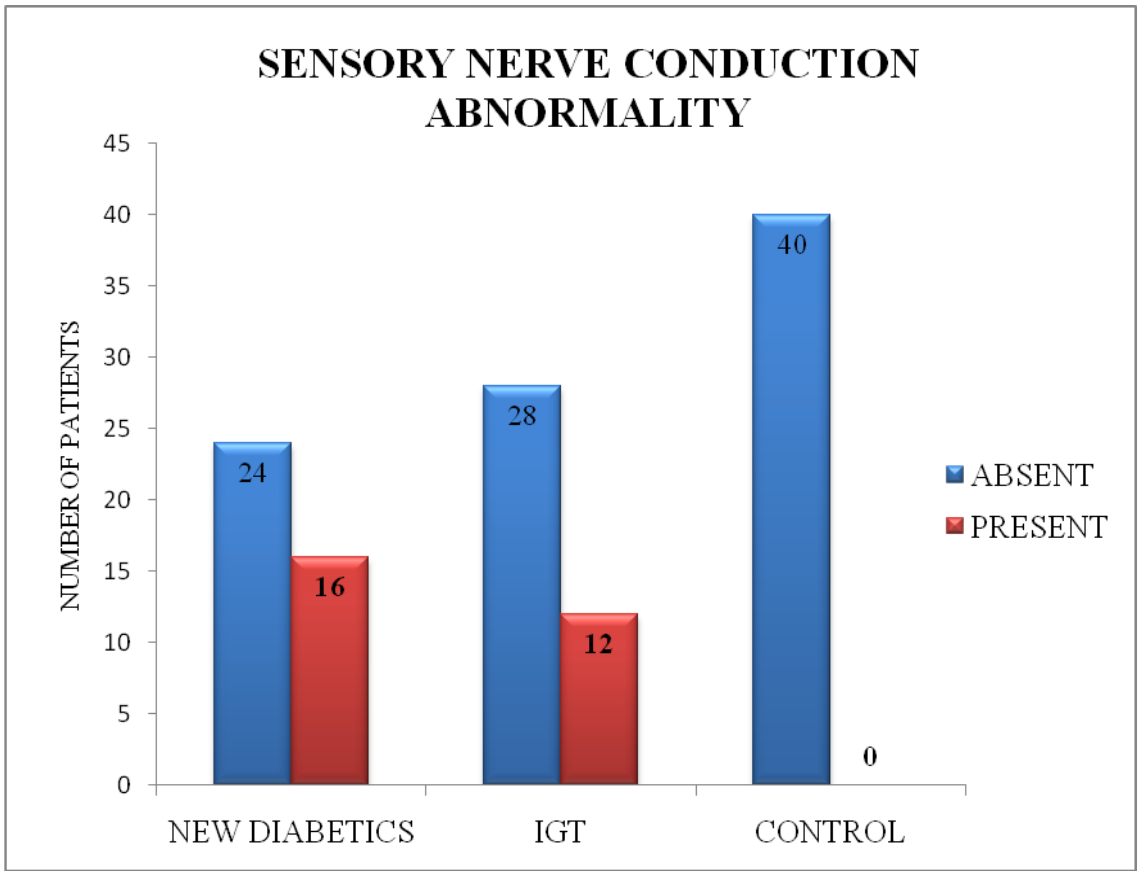
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NUMBER OF PATIENTS
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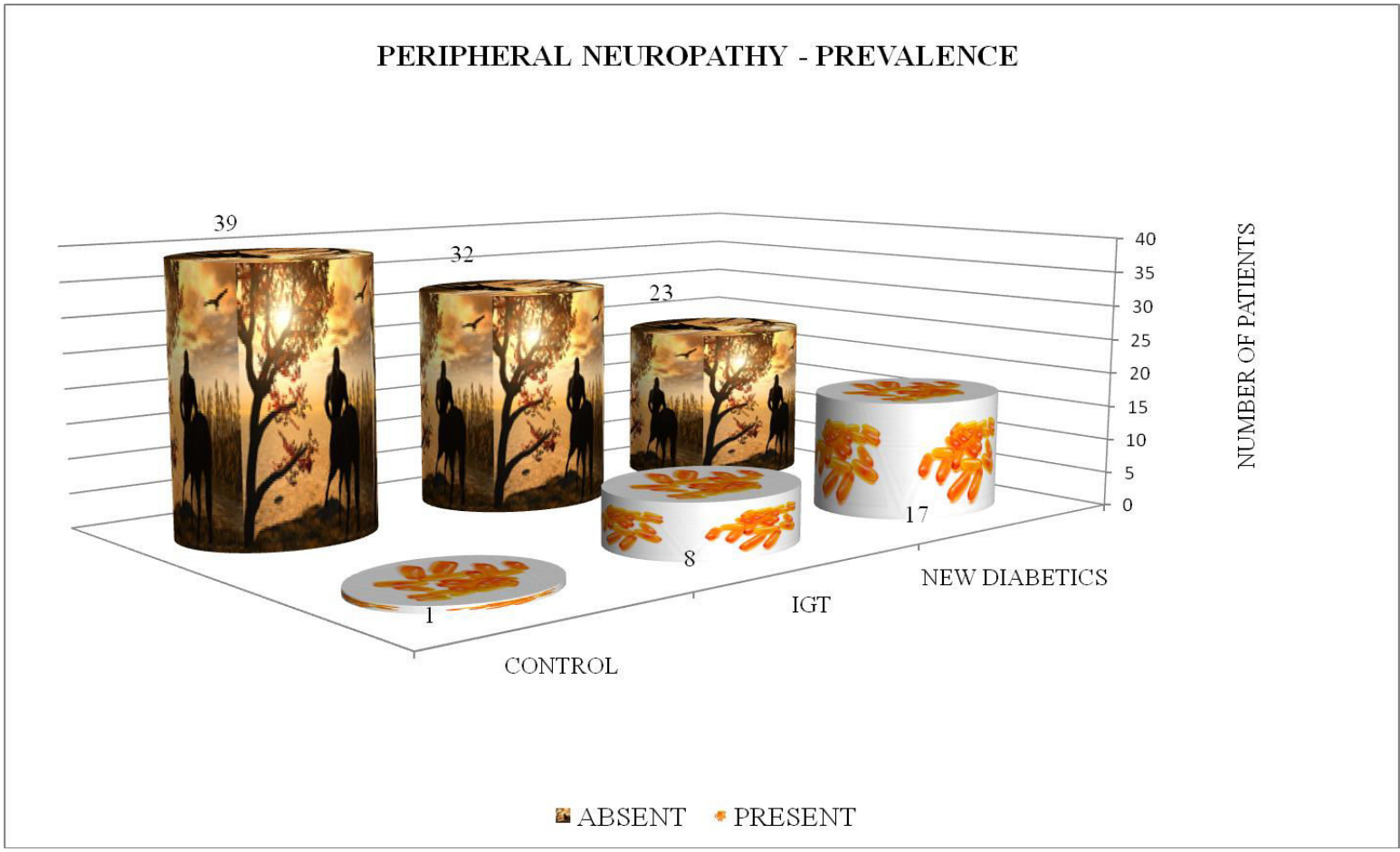
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CONTROL
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NEW DIABETICS
NUMBER OF PATIENTS
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ABSENT
PRESENT

STUDY OF PERIPHERAL NEUROPATHY IN NEWLY DETECTED DIABETES MELLITUS AND IN IMPAIRED GLUCOSE TOLERANCE

Name: Age:

Sex:

Address: Contact number:

Socioeconomic status: Occupation:

Educational Status:

HISTORY

Symptoms: ***Burning / tingling / cramps / gait disturbance / weakness /aching / numbess***

Joint pains/oral ulcers/rash

Decreased urine output/hematuria/pedal edema/fascial puffiness

Cough/hemoptysis/loss of appetite/loss of weight

NSS

PAST HISTORY

H/o hypertension	Y / N	H/o PTB, ATT	Y / N
H/o CAD	Y / N	H/o STD	Y / N
H/o Renal disease	Y / N	H/o hypothyroidism	Y / N

H/o CVA Y / N

PERSONAL HISTORY

Smoker : Y / N

Alcohol : Y / N

Drug abuse : Y / N .....

DIET : NV/V

FAMILY HISTORY

Hypertension :

Diabetes Mellitus :

Chronic Kidney Disease :

Neuropathy :

TREATMENT HISTORY :

EXAMINATION

Height -

Weight -

BMI -

signs of hyperlipidemia -

BP -

HR -

Pallor -

Pedal Edema -

Peripheral pulses -

Chest -

CVS -

P/A -

CNS Timed vibration Pin Prick

Ankle jerk

Temperature

NDS

INVESTIGATIONS

RBS

FBS

PPBS

GTT

HbA1c

Nerve conduction study

ABBREVIATIONS

ARI	Aldose reductase inhibitor
ADA	American Diabetic Association
ATP	Adenosine Triphosphate
AGE	Advanced glycation end product
AT II	Angiotensin II
AD	Anno Domini
BP	Blood Pressure
BC	Before Christ
BMI	Body Mass Index
CTS	Carpal Tunnel Syndrome
CIDP	Chronic inflammatory demyelinating neuropathy
CURES	Chennai Urban Rural Epidemiological study
DM2	Type 2 Diabetes Mellitus
DCCT	Diabetes Control and Complications Trial
DPP	Diabetes Prevention Programme Study

EDTA	Ethylene diamine Tetra Acetic Acid
EP	Electrophysiology
ED	Erectile Dysfunction
FPG	Fasting Blood Glucose
FBS	Fasting Blood Sugar
PPBS	Post Prandial Blood Sugar
GDM	Gestational Diabetes Mellitus
GADPH	Glyceraldehyde 3 phosphate dehydrogenase
GAD	Glutamic Acid Decarboxylase
HPLC	High Performance Liquid chromatography
HbA1c	Glycosylated hemoglobin
IENF	Intra Epidermal Nerve Fibre Density
IGT	Impaired Glucose Tolerance
IFG	Impaired fasting Glucose
NGT	Normal Glucose tolreance
LGA	Large for Gestational age
LA	Lipoic Acid

MAPK	Mitogen Activated Protein Kinase
MNSI	Michigan Neuropathy Screening Instrument
MNCV	Motor Nerve Conduction Velocity
MONICA/KORA	Monitoring of Trends and Determinants in Cardiovascular Disease Cooperative Research in the Region of Augsburg.
NAD	Nicotineamide Adenine Dinucleotide
NSS	Neuropathy Symptom Score
NDS	Neuropathy Disability Score
NO	Nitric Oxide
NCV	Nerve conduction Velocity
OGTT	Oral Glucose Tolerance test
OHA	Oral hypoglycaemic Drugs
PKC	Protein kinase C
PDE	Phosphodiesterase inhibitor
PCOS	Polycystic Ovarian Disease
QST	Quantitative sensory Testing

ROS	Reactive Oxygen Species
RAGE	Receptors for Advanced Glycation End Products
RCT	Ranomised Control Trial
SNCV	Sensory Nerve conduction Velocity
SNAP	Sensory Nerve Action Potential
VPT	Vibration Perception Threshold
VEGF	Vascular Endothelial Growth Factor
UKPDS	United Kingdom Diabetic Prospective Study
WHO	World Health Organisation
&	And
mg/dl	milligram per decilitre
yrs	years
±	plus or minus

MASTER CHART ABBREVIATIONS

Socio	-	Socioeconomic status
NSS	-	Neuropathy Symptom Score
HT	-	Hypertension
DM	-	Diabetes Mellitus
CAD	-	Coronary Artery disease
CVA	-	Cerebrovascular Accident
RENAL	-	Renal Disease
NV	-	Nonvegetarian
BMI	-	Body mass index
BP sys	-	Systolic blood Pressure
BP dias	-	Diastolic blood Pressure
NDS	-	Neuropathy Disability Score
FBS	-	Fasting Blood Sugar
PPBS	-	Post Prandial Blood Sugar
NCS	-	Nerve conduction Study

PTN	-	Tibial nerve
MNCV	-	Motor nerve Conduction Velocity
CMAP	-	Compound Muscle Action Potential
CPN	-	Common Peroneal Nerve
SNCV	-	Sensory Nerve Conduction Velocity
SNAP	-	Sensory Nerve Action potential
ABN	-	Abnormality

NEUROPATHY 0 - Absent

1 - Present

SEX M - Male

F - Female

Age Group

1 = 20-30

2 = 31 - 40

3 = 41-50

4 = 51 and above

Family History of Diabetes/Hypertension

Y = Yes

N = No

Socio economic status Low lower socioeconomic status

Mid middle socioeconaomic status

Smoking Y = Yes

N = No

Nerve conduction ABN - Abnormality Y= Yes

N =No

Past history of HT/CAD/CVA/Renal disease/Smoking –

Y = Yes

N = No

Diet Non vegetarian - Y= Yes

N =No